ESTABLISHING A NEW-VACCINE INTRODUCTION UNIT IN ETHIOPIA

A Scoping Review

February 2020

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The Ethiopian Academy of Sciences

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ACRONYMS

ADI	Addis Declaration on Immunization
AEFI	Adverse Effect Following Immunization
AIDS	Acquired Immunodeficiency Syndrome
AOM	Acute Otitis Media
BCG	Baccilus Calmette-Guerin
BMGF	Bill and Melinda Gates Foundation
BRICS	Brazil, Russia, India, China, South Africa
CDC	Centers for Disease Control and Prevention
COI	Conflict of Interest
cGMP	current Good Manufacturing Practice
CSA	Central Statistics Agency
DNA	Deoxyribonucleic Acid
DoVC	Decade of Vaccines Collaboration
DPT	Diphtheria Pertussis Tetanus
EDHS	Ethiopian Demographic and Health Survey
E-ITAG	Ethiopian NITAG
EOS	Enhanced Outreach Strategy
EPI	Expanded Program on Immunization
EVA	Epidemic Vaccine for Africa
eVIN	electronic Vaccine Intelligence Network
FDRE	Federal Democratic Republic of Ethiopia
GAP	Global Action Plan
GAVI	Global Alliance for Vaccine Initiative
GDP	Gross Domestic Product
GHVE	Global HIV Vaccine Enterprise
GHSA	Global Health Security Agenda
GIVS	Global Immunization Vision and Strategy
GNI	Gross National Income
GNN	Global NITAG Network
GPEI	Global Polio Eradication Initiative
GVAP	Global Vaccine Action Plan
HC	Health Center
HEW	Health Extension Worker
Hep B	Hepatitis B
HRSA	Health Resource and Supplies Agency
Hib	Haemophilus influenzae type b
HIC	High Income Countries
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HPs	Health Posts
HRH	Human Resource for Health
HSS	Health System Strengthening
HSTP	Health Sector Transformation Plan
ICC	Inter-Agency Coordinating Committee
IPD	Invasive Pneumonia Disease
IPV	Inactivated Polio Virus
IVR	Initiative for Vaccine Research
JE	Japanese Encephalitis
KII	Key Informant Interview
LIC	Low-Income Countries
LMIC	Low-Middle Income Country
MCV2	Measles-containing-vaccine second-dose
MDG	Millennium Development Goal
MDR	Multidrug Resistant
MIC	Middle Income Country
MoFEC	Ministry of Finance and Economic Cooperation
MoH	Ministry of Health
MPAC	Malaria Policy Advisory Committee
NAGI	National Advisory Group on Immunization

NCD	Non-Communicable Diseases
NDOH	National Department of Health
NIP	National Immunization Program
NITAG	National Immunization Technical Advisory Group
NP	Nasopharyngeal
NRAs	National Regulatory Authorities
NRC	NITAG Resource Center
NTD	Neglected Tropical Disease
NUVI	New and Underutilized Vaccine Initiative
ODA	Official Development Assistance
OPV	Oral Polio Vaccine
PCR	Polymerase Chain Reaction
PCV	Pneumococcal Conjugate Vaccine
PCV10	10-valent Pneumococcal Conjugate Vaccine
PHC	Primary Health Care
PENTA	Pentavalent Vaccine
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analysis
R&D	Research and Development
RED	Reach Every District
RITAG	Regional Immunization Technical Advisory Group
RV	Rotavirus
SAGE	Strategic Advisory Group of Experts
SIAs	Supplemental Immunization Activities
SIVAC	Supporting Independent Immunization and Vaccine Advisory Committees
SMART	Strategic Multi-Attribute Ranking Tool for Vaccines
SOS	Sustainable Outreach Services
SP	Streptococcus Pneumoniae
SSFFC	Substandard/spurious/ falsely labeled/ falsified/counterfeit
STIs	Sexually Transmitted Infections
TB	Tuberculosis
Td	Tetanus and diphtheria
Tdap	Tetanus, diphtheria and acellular pertussis
TPPs	Target Product Profiles
TT	Tetanus Toxoid
UNDP	United Nations Development Program
UNICEF	United Nations Children's Fund
USAID	United States Agency for International Development
VERA	Vital Events Registration Agency
VPA	Vaccine Procurement Assistance
VPB	Vaccine Procurement Baseline
VPPAG	Vaccine Presentation and Packaging Advisory Group
WB	World Bank
WCV	Whole-Cell Vaccines
WHO	World Health Organization
WPV	Wild Polio Virus

EXECUTIVE SUMMARY

Immunization is recognized as one of the most successful and cost-effective health interventions known. Current trends involving evolution of new strains, prolonged and more frequent epidemics, increased antimicrobial resistance, and awareness of the role of climate change on the global burden of diseases and related innovations in vaccines has returned the vaccine issue to the forefront of global public health discussions.

Immunization, one of the earliest forms of introduction of modern medicine in Ethiopia, has recorded major achievements since the introduction of the Expanded Program of Immunization (EPI) in 1980. However, immunization coverage remains very low in pastoralist areas in particular, 23%, 30.7%, and 45.6% in Afar, Somali, and Gambella, respectively, compared to the national coverage of 65.7%. Furthermore, Ethiopia is under considerable internal and external pressure to adopt new and underutilized vaccines.

The adoption of new vaccines and related technologies present several challenges and involves a complex decision-making mechanism and processes that require thorough analysis and understanding. Therefore, this study was undertaken by the Ethiopian Academy of Sciences (EAS) to document and propose mechanism(s) for establishing/strengthening new vaccine introduction unit in the country.

The Study Group conducted a scoping review of the published literature using the Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA) strategy. Publications in major databases were searched using defined search terms. A total of 192 articles were selected for full-text review form among 1,165 articles identified. A key informant interview of selected participants from government, the academia, and multilateral organizations was conducted. A report and policy brief were developed, reviewed by three participating sister Academies, and discussed at a consensus-building workshop involving key stakeholders.

The review identified that 10 vaccines are currently in use in the public sector in Ethiopia, including Baccilus Calmette-Guerin (BCG), Diphtheria, Pertussis, Tetanus, Polio 1 (IPV2), Measles, hepatitis B (hepB), Hemophilus influenzae Type b (Hib), rota, and Pneumococcal Conjugate Vaccine (PCV). Others, such as cholera, rubella and rabies are used during outbreaks and to avert transmission to exposed patients. Ethiopia intends to introduce a few more including meningococcal meningitis and yellow fever vaccines.

A number of ***New/new generation Vaccines*** could be available in the near future, like vaccines against dengue, malaria and neglected tropical diseases (NTDs) or underutilized vaccines against cholera etc. Over 20 vaccines are in clinical trials or advanced pre-clinical development. With the growing threat of multidrug resistant (MDR) tuberculosis (TB), support for the development of new TB vaccines remains a priority. Several innovative influenza vaccine candidates and next-generation of vaccines for *Neisseria meningitidis and Streptococcus pneumoniae* are being developed.

Globally, there is, unprecedentedly large pledged funding by the Global Alliance for Vaccine Initiative (GAVI), Ethiopia being in a very favorable position. New and underutilized vaccines initiative (NUVI) in Ethiopia presents undeniable promises of better health outcomes. Extensive health coverage has been achieved through the Health Extension Program (HEP) and increasing numbers of health centers (HC) and hospitals. There are also a number of barriers to consider viz. infrastructure, migration, conflicts, health services quality, and health workforce density and skills.

Foremost among ***Challenges of introducing new vaccines*** are consistent and predictable financing of the new vaccines. Sustaining immunization financing requires strengthening the programs through budget reforms, decentralization, legislation and innovative approaches. Health system related issues such as competing priorities, lack of adequate data on cost-effectiveness and lack of surveillance systems to support new vaccine introduction should be addressed. Additional costs for staff training, distribution of vaccines and logistics and social mobilization activities hamper progress to achieve high immunization coverage.

There is increasing and concerted global, regional and national commitment to vaccine procurement and access. New vaccines introduced in Ethiopia to date have encountered limited challenges. Collaboration between philanthropists and the World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) has meant that more new vaccines can be introduced more rapidly. Improved collaboration among partners and stakeholders (e.g. industry and academia, human and veterinary vaccine developers) will allow more rapid application of promising approaches and technologies in the development of vaccines. The Ethiopian Public Health Institute (EPHI) has previous experience in producing bacterial and viral vaccines. For instance, during cholera epidemics in the 1960s, the Institute used to produce a parenterally administered killed whole cell vaccine. The Institute also produced smallpox and typhoid fever vaccine in early 1950. Furthermore, Fermi type rabies vaccine has been produced by the Institute for over four decades both for human and animal use and it is still in use in the country. To replace this outdated vaccine with cell culture-based rabies vaccine. EPHI adapted this new technology and has transferred the cell culture-based

rabies vaccine production to New vaccine Initiative (NVI) destined for mass vaccination of source animals. The experience of NVI and the emerging biomedical and biotechnology initiatives may be used for developing new vaccines in country.

As recommended by WHO, strong, independent and inter-disciplinary National Immunization Advisory Groups (NITAGs) are essential as the experience of South Africa illustrates. Ethiopia, which has, in May 2016, established the Ethiopian - National Immunization Advisory Group (E-NITAG), has an opportunity to learn from its positive experience in introducing new vaccines like PCV and rota vaccine. Consultation with Inter-agency Coordinating Committee (ICC) and broader engagement involving other key stakeholder like the Ministry of Finance and Economic Cooperation (MoFEC) will be required.

Political commitment is central to success in the introduction of new vaccines. Other drivers include availability of funding, political prioritization of vaccines or the vaccine-preventable diseases and the burden of disease. Ideally, decision should be based on a systematic review of data on the magnitude and cost of the disease as well as vaccine safety, efficacy, cost-effectiveness, and programmatic feasibility in the context of a specific country. The process requires strong leadership and coordination to ensure availability of adequate and timely funding. Country-specific introduction plans are required covering selection of vaccine products, decision on eligibility and immunization schedules, preparation for introducing vaccines, program monitoring & evaluation, and implementation research.

Conclusions: In spite of the track records of immunization in improving health outcomes, there still are challenges with coverage, equity and quality of immunization services in Ethiopia. With increasing number of new and improved vaccines becoming available, there will be continued pressure to adopt new and improved vaccines and delivery technologies. Introduction of new vaccines into routine programs will become more frequent and complex and issues of prioritization and sustainability are bound to emerge. As the health/vaccine delivery system in Ethiopia exhibits several weaknesses, it can easily be overburden by too ambitious introduction of new vaccines and/or new procedures.

Successful introduction of new vaccines will require integration with other intervention programs. The immunization program requires clear mandates and mechanisms to finance and monitor services. The program needs to introduce new vaccines guided by sound evidence base on the epidemiology and burden of disease, safety, efficacy and relative cost-effectiveness of the vaccine and base decisions on wide-reaching analyses of technical, political and programmatic considerations. In spite of promising global commitments, measures should be taken to meet anticipated financial flow gaps for vaccination in the

future. The E-NITAG should be strengthening to support mechanism for adequate vaccine intelligence in the country.

1. BACKGROUND

"The obligations of the state to provide quality immunization services to all, and the duties of each individual to be vaccinated or ensure that their children are vaccinated, are at the heart of accountability in the immunization program" (WHO AFRO 2017).

1.1. General

Immunization (Table 1.1) is recognized as one of the most successful and cost-effective health interventions known (WHO 2013, Kling et al. 2014, Mihigo et al. 2016, Ozawa et al. 2016, Horton et al. 2017). It has greater impact on global health than any other medical intervention (MacLennan & Saul 2014), saving millions of lives (Jit & Hutubessy 2016, Pagliusi et al. 2016).

Table 1.1: Return, per dollar, on investment for Immunization, by antigen, in 94 low and middle Income countries, 2011–20

Measles	Yellow Fever	Men A*	Hib	HepB	Sp	JE	HPV	Rubella	Rotavirus
58.23	13.23	11.19	9.62	9.42	3.13	3.01	2.91	2.02	1.31

*Source: Ozawa et al 2016) *Men A is Neisseria meningitidis serogroup A. Hib is Haemophilus influenzae type b. Hep B is hepatitis B. Sp is Streptococcus pneumoniae. JE is Japanese encephalitis. HPV is human papillomavirus*

Vaccines could serve all age groups and become the most efficient 'life insurance' of the twenty-first century, contributing to a disease-free life of longer duration and better quality for many members of modern societies (Kochhar & Seeber 2013, Rappuoli et al. 2011). In addition to health, the widespread implementation of immunization leads to improved economic development (MacLennan 2013), even though study designs require improvement (Jit et al. 2015). In spite of these demonstrable successes, infectious diseases continue as major threats to health in low income countries. However, there is a concern that inadequate access to vaccines is responsible for over two million deaths annually in low- and middle-income countries (Kochhar & Seeber, 2013). In countries such as Ethiopia, there are problems with adequate coverage with existing vaccines (Arora et al. 2013, Cutts et al. 2013, Nelson et al. 2016, Restrepo-Méndez et al. 2016, Danovaro-Holliday et al. 2018

) and significant delays/challenges in introducing new ones (Gordon, 2012, Mihhigo et al. 2017). Although much has been done to narrow the gap of accessibility to vaccines for the world's poorest people, an international concerted effort is needed to make the promise of new vaccines a reality.

The ongoing dynamic epidemiology of diseases, involving evolution of new strains, prolonged and more frequent epidemics, increased antimicrobial resistance, and awareness of the role of climate change on the global burden of diseases has returned the vaccine issue to the forefront of global public health discussions (Shin et al. 2011). Of an estimated 5.6 million deaths each year (15,000 per day) in children under 5 years of age, 15–25% are attributable to vaccine-preventable diseases (Loharikar 2018), and, to date, there are not effective vaccines against major problems such as malaria, TB and HIV (Kling et al 2014).

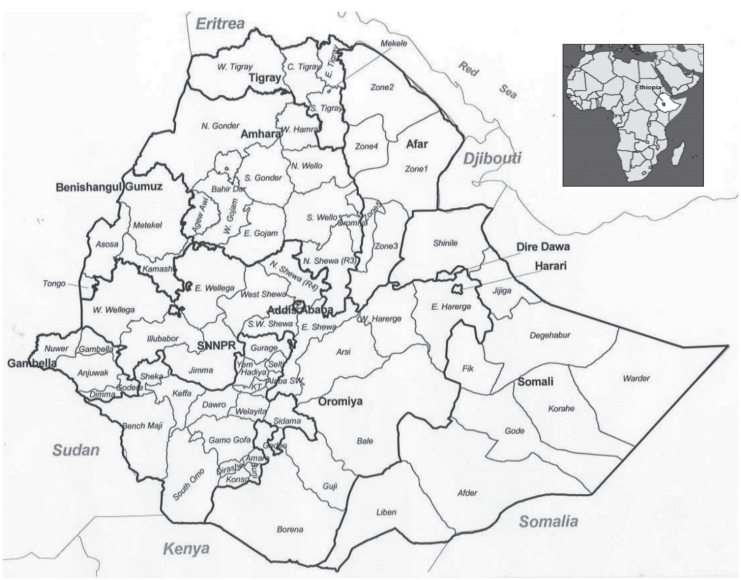
1.2. Immunization Situational Analysis, Ethiopia[1]

Ethiopia is a large - 1.1million km^2 (Map 1,1), low-income country (Box 1.1), over 100 million people, 40.6% under 15 years of age (Table 1.2), over 80% rural, with major challenges of providing equitable health services to a highly diverse (over 80 ethnic groups) and dispersedly settled population.

Box 1.1: Ethiopia Development Status:

- GNI / capita (US$): 740
- GDP / capita (US$): 1'899
- Infant (<12 months) mortality rate: 41
- Child (<5 years) mortality rate: 58

(Source: WHO 2018)



Map 1.1: Regional States and Zones, Ethiopia, 2007

1 Based mostly on MOH 2015 and Belete et al 2015, see for detailed references

Table 1.2: Population data in thousands, 1980-2017 *(Source: WHO 2018)*

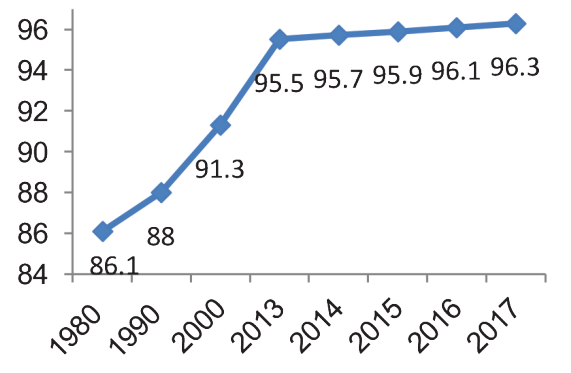
	2017	2016	2015	2014	2013	2000	1990	1980
Total population	104,957	102,403	99,873	97,367	94,888	66,537	48,087	35,265
Births	3,284	3,258	3,230	3,200	3,167	2,915	2,297	1,751
Surviving infants	3,161	3,130	3,098	3,063	3,025	2,660	2,021	1,507
Pop. less than 5 years	15,366	15,177	14,901	14,689	14,459	12,410	9,102	6,690
Pop. less than 15 years	42,564	42,088	41,558	41,096	40,604	30,929	22,259	15,917
Female 15-49 years	25,857	24,991	24,150	23,293	22,453	14,686	10,603	7,936

The country's health system is decentralised, with authority devolved to the Regional Health Bureaus (RHBs), Zonal Health Departments (ZHDs) and Woreda Health offices (WoHOs). Vaccine preventable diseases account for a substantial portion of under-five mortality with pneumonia, diarrhoeal disease and measles among the leading causes.

Immunization was one of the earliest forms of introduction of modern medicine in Ethiopia. The country started smallpox vaccination in the mid-1800s and childhood immunization in the late 1940s, well before it took a major immunization drive for smallpox eradication (Kitaw et al. 2017). The Ethiopian EPI was launched in 1980, with six antigens namely BCG, Diphtheria, pertussis, tetanus, polio and measles and with the objective of 100% coverage of children under two years. In 1986, the coverage target was reset to 75% and the target age group changed to children less than one year of age.

From 1980 up to 2003, the country's vaccination coverage was rather low and erratic, reflecting major socio-political events such as government transitions and the Ethiopia-Eritrea war. However, coverage has shown gradual increase with the introduction of the Reach Every District (RED) and Sustainable Outreach Services (SOS) approaches and the health extension program in 2003. Ethiopia has thus been classified as one of the countries achieving the greatest increases in diphtheria, pertussis, tetanus 3 (DPT3) vaccine coverage but with large number of under-vaccinated children (WHO 2018b). All these have contributed to increased infant survival (Fig. 1.1).

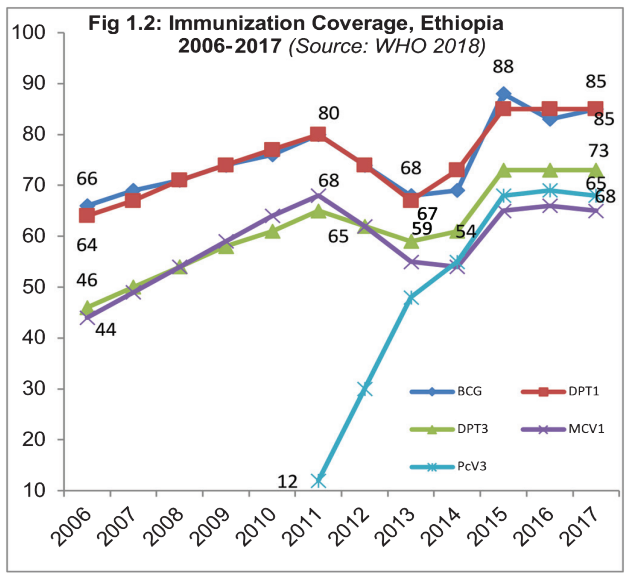
Fig 1.1: Percentage of Surviving Infants, 1980-2017 *(Source: Adapted from WHO 2018)*

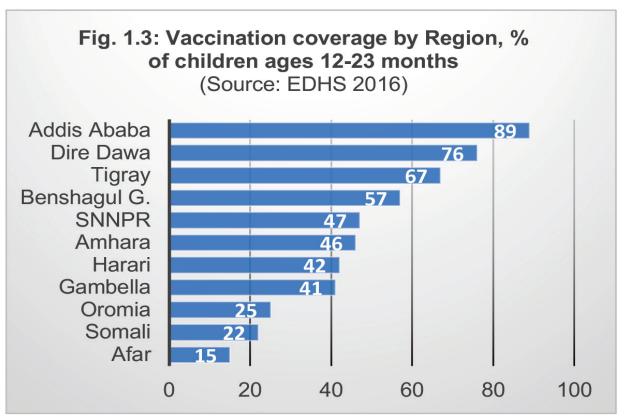


Attempts are being made to mitigate remaining system-wide barriers related to geographic coverage through approaches such as the Enhanced Outreach Strategy (EOS). However, there are number barriers to vaccination including shortages in vaccine supplies, non-functional refrigerators, and lack of efficacy, cost–effectiveness information, and technical assistance to support with introduction. There are also issues with logistics, supply and quality control, training, availability of health posts to deliver services, and low awareness among mothers and caregivers about the importance of immunization, and lack of funding for vaccines (Bezunesh et al. 2013, Zewdie et al. 2016, Kochhar et al. 2013).

More generally, poor infrastructure and difficult topography, inequitable access and poor quality of services in these areas have not been well addressed. Thus, in spite of significant improvements in recent years, immunization coverage remains low (Fig 1.2 & 1.3) with 188 (22%) of districts with less than 80% coverage (Table 1.3).

Immunization coverage remains very low in pastoralist areas in particular. The national routine EPI coverage survey conducted in 2012 showed that the penta 3 coverage of pastoralist regions[2] notably Somali, Afar and Gambella were 30.7%, 23% and 45.6% as compared to the national coverage of 65.7%.



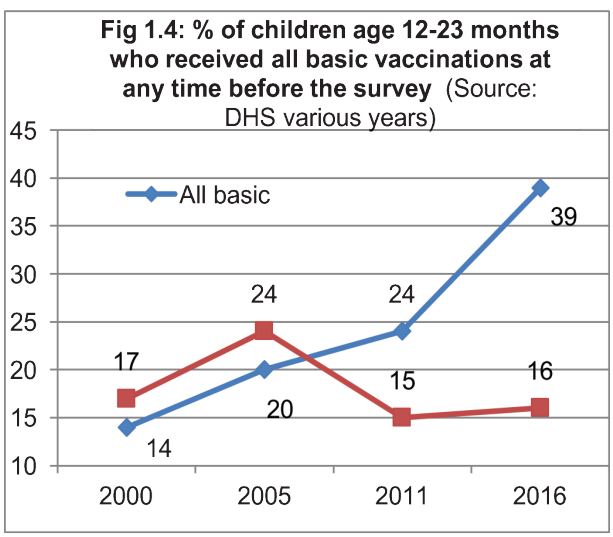


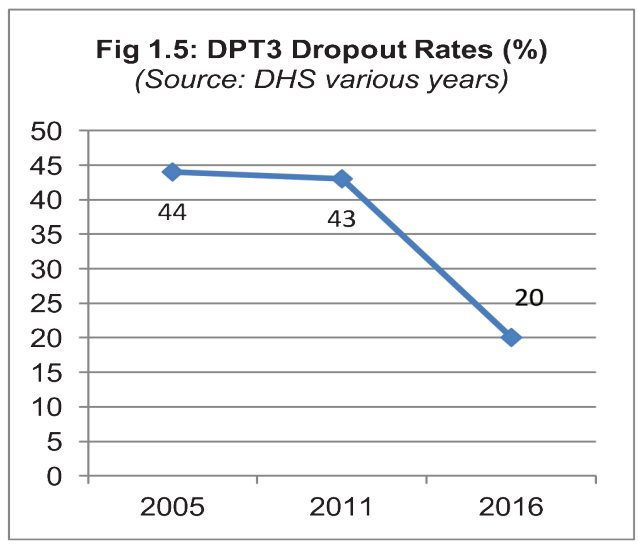
2 "The Enhanced Routine Immunization Activity (ERIA)… used "community champions" to encourage nomadic, pastoral families to have their children vaccinated and introduced new approaches such as task shifting to improve service delivery to these hard-to-reach populations… WHO facilitated a partnership among political and religious leaders, government health offices, non-governmental organizations, UNICEF and other partners – by, for example, organizing a regional interagency coordinating committee - to win local support, expand the health workforce and plan and implement a vaccine delivery plan to meet local conditions." (WHO 2012).

Table 1.3: Districts by DPT3 coverage reporting Status *(Source: WHO 2018)*

	Number	%
Proportion of districts reporting DPT3 coverage:	**854**	**100**
Greater or equal to 90%	529	62
From 80 to 89%	137	16
From 50 to 79%	154	18
Less than 50%	34	4
Proportion of districts not reporting DTP3 coverage	**0**	**0**
Total (number)	**854**	**100**

EDHS 2016 (Fig. 1.4) shows that the percentage of children age 12-23 months who received all basic vaccinations at any time before the survey was 15% Afar, 22% Somali and 25% Oromia compared to the national coverage of 39% (CSA 2017). Thus, Ethiopia continues to have some of the largest numbers of children who did not receive 3 DPT doses (Casey et al 2017, Feldstein et al 2017). DPT3 dropout rate (>10%, Fig. 1.5) was high (WHO 2018).





In recent years, related to acceleration in the development of new vaccines (Moxon & Siegrist 2011), there has been significant increase in new vaccines introduction (Williams et al. 2016, Kochhar & Seeber 2013, Dutta et al. 2016). To date, Ethiopia has introduced only 10 [Ministry of Health (MOH) 2015)] of some 25 licensed vaccines available (Lee & McGlone 2010, WHO 2013, Loharikar et al. 2016, Loharikar 2018). There are also a number of new vaccines in the pipeline.

Hepatitis B and *Haemophilus influenzae* type B vaccines were introduced to the routine immunization program in 2007 and pneumococcal-10 and rotavirus[3] vaccines in 2011 and 2013, respectively. There were plans to introduce Inactivated Polio Virus (IPV), measles-rubella, meningitis and yellow fever vaccines for less than one year children and Human Papilloma Virus (HPV) and Td vaccines by 2019 (MoH 2015). Sheep brain derived Fermi type rabies vaccine is manufactured in country and utilized for the majority of exposed patients and a replacement production of a safer and effective cell culture based anti-rabies vaccine is planed (Hurisa et al 2013). A global health security agenda roadmap (2015-2019), incorporating most of these, has been prepared (GHSA 2016).

Ethiopia is heavily reliant on a large number of partners' funding for financing its immunization program, including funds from bilateral and multilateral partners, Private contributions, and non-governmental organizations. Partner funds cover costs for vaccines, training, supervision, monitoring, a share of capital expenses, and supplementary immunization activities. The government has secured a budget line for EPI that funds some traditional routine vaccines such as BCG, TT and 50% of polio vaccines as well as country co-financing of the newly introduced vaccines (PCV and rotavirus vaccines). Salary of healthcare workers providing immunization and other services and a limited capital budget is financed by the Government of Ethiopian (GoE). The main funding partners for immunization include the GAVI Alliance, UNICEF, the United States Agency for International Development (USAID), Netherlands and the government of Japan.

Ethiopia has a relatively long history of immunization legislation with some of the first edicts by Emperors Yohannes IV (1872-1889) and Menelik II (1889-1911) being on smallpox vaccination. Subsequently regulations on travel/visa requirements, EPI etc. have been issued but enforcement has been largely deficient (Kitaw et al. 2017). Even as late as 2004, a text book for Health Extension Workers (HEW) wrote "The HEW, when faced with regulations that are too advanced may find it advisable to enforce only part of that rule which is to some extent applicable and leave the remainder for a later date, when health condition are more advanced" (Jira 2004[4]).

Health facilities, usually Health Posts (HPs), are expected to "issue a vaccination certificate at around nine months, after the completion of immunizations, to be presented on enrollment

3 The rotavirus vaccine is among those recently introduced in Ethiopia. Its demonstrated cost-effectiveness in reducing population hospitalization burden elsewhere in developing settings has been a strong argument for its widespread utilization in low-income, high-burden settings (Bar-Zeev et al 2016). It is very effective in terms of efficacy, cost and safety against diarrhoea caused by rotavirus and highly recommended for consideration for inclusion in EPI programs of developing countries (Ghazanfar et al 2014).

4 See for list of legislations.

for school" (WB 2016). However, in the absence of a centrally coordinated vital registration system, ensuring proper tracing of immunization has proved a daunting task. The passing of "A Proclamation on the Registration of Vital Events and National Identity Card" No. 760/2012 and the establishment, in 2014, of the Vital Events Registration Agency (VERA) which began to issue birth and death certificates and record other vital events in August 2016 promises a major transition in establishing unique identity (WB 2016).

Vaccine/ immunization regulation is a complex process and requires regular updating and even though the MOH (2015) claims to have "legislation or other administrative order establishing a line item for vaccines" and "legislation identifying the sources of public revenue for immunization financing". More work will be required to ensure the six regulatory functions defined by WHO to assess, monitor, and improve national regulatory authorities (Box 2.1). Vaccine regulations have to be harmonized and standardized with global requirements (WHO et al. 2009). There is need, therefore, for strong advocacy effort on parliament and other representative bodies to "enact legislation that mandates the introduction of new vaccines, approve and amend the budgets for immunization programs, establish financing mechanisms for immunization services, and oversee the implementation of new immunization-related policies" (R4D 2017). Some countries have moved from 'recommended' and made child immunization mandatory (Bennie 2017).

Box 1.2: WHO Regulatory Functions:

1. Published set of requirements for licensing (of products and manufacturers)
2. Surveillance of vaccine field performance (safety & efficacy)
3. System for batch or lot release
4. Use of the laboratory, when needed
5. Regular manufacturers inspection for good manufacturing practice compliance
6. Evaluation of clinical performance through authorized clinical trials

(Source: Milstien & Belgharbi 2004)

1.3. Purpose of the Scoping Review

The pace of development of new vaccines is accelerating more than ever before. (Moxon & Siegrist 2011, Kitaw 2015). A doubling of some 20 vaccines available to date is expected in the next few years, including vaccines from the hitherto uncharted fields of parasitic and fungal infections. Traditionally, it has taken decades to introduce new interventions in low-income countries. Several factors account for these delays, one of which is the absence of a framework to facilitate comprehensive understanding of the processes to inform policy makers and stimulate decision-making in adopting new vaccines (Romore et al. 2016). There has been considerable pressure to adopt new and underutilized vaccines initiative (NUVI) as early as possible, particularly since the 61st World Health Assembly decision in May 2008

(WHO 2008). Subsequently, there has been a general consensus that decisive support for new vaccine introduction in low- and middle-income countries is critical to guiding the efficient use of resources and prioritizing high impact vaccination programs (de Oliveira et al. 2013, Jauregui et al 2015). However, several challenges persist because decision-making is a relatively little understood process, new vaccines tend to be more expensive, some 'hidden' but important problems may lack public/political attractiveness (Burchett et al. 2012) and most introductions are made under conditions for which low-income countries (LIC) have little experience in proactive planning (Gordon, 2012). There have been recent attempts to understand better the decision-making processes and impacts of the introductions of new vaccines and approaches (Molla et al. 2015, Tores-Rueda et al. 2015).

Even though immunization is recognized as one of the most successful and cost-effective health interventions, infectious diseases continue to pose major threats to health in the Ethiopia. There have been recent attempts to understand better the decision-making processes and impacts of introducing new vaccines but these need strengthening. The Ethiopian Academy of Sciences (EAS) established a study group consisting of experts in the fields of immunology, public health, pediatric and child health, and health economics. EAS also enlisted the collaboration of Ethiopian Young Academy of Science (EtYAS), the Ugandan Academy of Science (UNAS) and Sudanese National Academy of Science (SAS) to contribute to the study.

One of the strategic objectives of EAS is providing relevant advice to the GoE based on scientific evidence. The Academy has conducted numerous consensus studies and meetings on issues of national importance. Members of the Academy are highly experienced researchers with relevant expertise to undertake a study on vaccine intelligence system, develop a policy brief and disseminate findings. It also benefits from inputs form two sister academies (UNAS & SAS), which will also take this up in their respective countries.

This scoping review tries to assemble the lessons learnt and prospects in adoption of NUVI in the Ethiopian context. The study critically appraised existing national and international policies and institutional frameworks against scientific advances and consulted with national and global stakeholders to develop a report and a policy brief on establishing/strengthening a new-vaccine intelligence system in Ethiopia. A hard look at the facts and paving the way for a proactive planning is important as, in spite of ups and downs (Gordon 2012), there is an unprecedented pledged funding by the GAVI Alliance (Rees & Madhi 2011). Ethiopia has been in a very favorable position as the country, where GAVI has, since 2001, invested the highest amount in Africa. In addition, a previous evaluation (Alebachew & Ortendahl 2009) showed that the specific GAVI contribution to health systems strengthening was "greater than what would have been allowed under the HSS normal allocation formula i.e. $5 per newborn".

2. METHODS

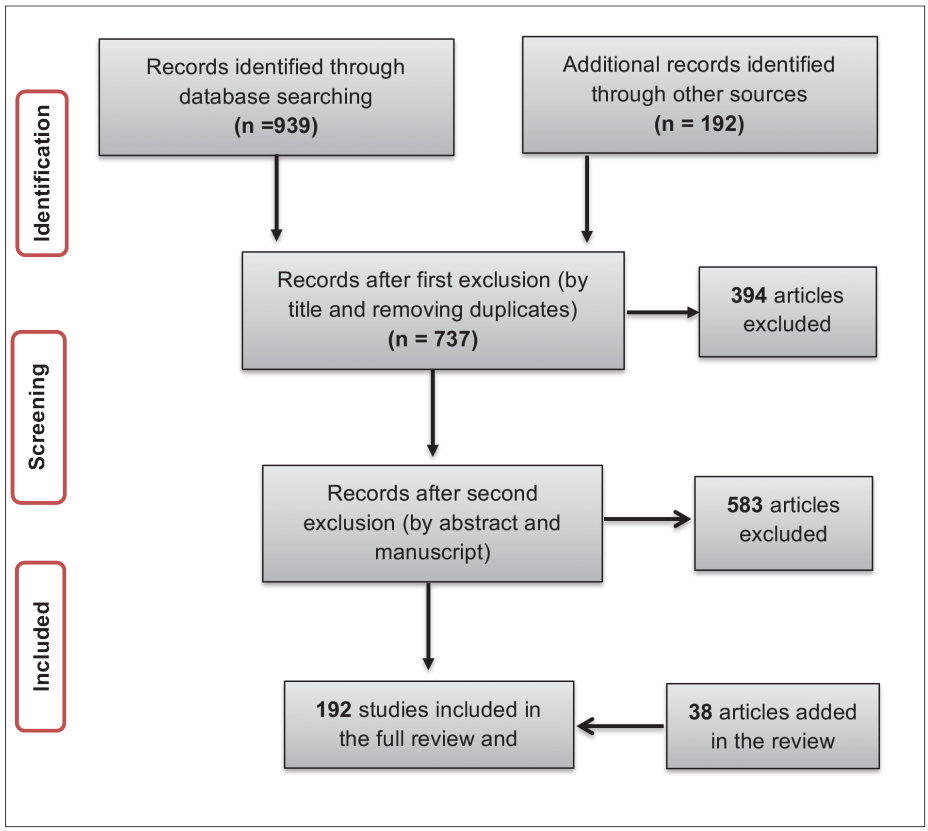
2.1. Scoping review

We conducted a scoping review of the published literature using the PRISMA strategy (Fig 2.1), which allows systematic selection of articles (Moher et al. 2009), to examine experiences related to new vaccine introduction. To this end themes for review based on preliminary review of the literature (Appendix 1) and semi-structured questionnaire for KII (Appendix 2) were developed. Four publication databases (Cochrane library, Pub-med, Embase and HINARI) were searched using vaccine and health system-related search terms/key words including: Introduction of vaccine; new vaccine; vaccine intelligence; introduction of new antigen; inclusion of new vaccine; adoption of new vaccine to a health system; inclusion of new antigen; developing countries; Ethiopia; BRICS.

All articles from the initial search strategy were included in the review. Two of the authors reviewed independently the titles and abstracts of each article retrieved though the search strategy. All articles on which both agreed and articles agreed upon after consultations were included. All articles felt to meet inclusion criteria by any of the sub-teams were included in the full-text review.

The search yielded 939 unique articles dating from 2010 to 2018. In addition, 192 articles were included from other sources during the background review. Based on review of the title and removal of duplicates, we found 737 potentially relevant articles, of which 154 were selected as relevant for full review based on review of the abstracts and manuscripts. Additional 38 articles were identified in the review process. Team members completed the full text review of a total of 192 selected articles.

Fig 2.1: Outcome of the Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA)



2.2. Key informant interviews

As a qualitative component of the survey, we were able to obtain responses from seven key informants we considered knowledgeable in the subject area. The key informant respondents were from the academia (3); health sector/regional health bureau (1); multi-lateral health institution (1); and professional associations (2). All the informants were among the most senior professionals in the country in terms of research, experience and consultation with the sector and within the specific subject area of inquiry.

We analyzed the responses from the key informants according to their thematic contents by tabulating a thematic grid. The themes for the analysis included overall strengths, weaknesses, opportunities and threats (SWOT); issues of coverage; financing and sustainability; possibility and modality of introducing new vaccines; logistics and supply management; new vaccines envisaged for introduction in the near future, and the need for establishing a vaccine introduction unit. We have integrated the results of the thematic content analysis within those of the scoping review.

3. CURRENTLY AVAILABLE

3.1 Vaccines Currently in use in Ethiopia

As indicated below, Ethiopia has introduced 10 of the currently available vaccines (Table 3.1) using the WHO recommended schedule (Table 3.2). The country intends to introduce a few more including inactivated Polio Virus (IPV), measles-rubella, meningitis and yellow fever vaccines for children less than one year of age, and Human Papilloma Virus (HPV) vaccines for 12-13 year old children by 2019 (MOH 2015). Others, such as cholera, rubella, and rabies are used during out breaks or ongoing transmission and to exposed patients (Levine et al. 2016, Hurisa et al. 2013, MOH 2015). While not all are applicable to the Ethiopian context (disease burden etc.), a number, those supported by GAVI in particular (Table 3.1), could be introduced in the near future.

Table 3.1: Available Vaccines, Year Introduced in Ethiopia and GAVI Support Status

	Vaccine	Year Introduced in Ethiopia [a]	GAVI Support Status [b]		
			Current support	Planned, not yet budgeted	Not yet planned
1	BCG[1c]	1980	☆		
2	Diphtheria[1]		☆		
3	Pertussis[1]		☆		
4	Tetanus[1]		☆		
5	Polio[1] (IPV[2])		☆		
6	Measles[1]		☆		
7	Chikungunya[3]				☆
8	Cholera[3]				☆
9	Dengue[3]				☆
10	Hepatitis A				☆
11	hepatitis B[2]	2007	☆		
12	Hib[2]	2007	☆		
13	HPV[2]	2019 (Planned)	☆		
14	Influenza[2]				☆
15	Japanese encephalitis[3]			☆	
16	MCV2			☆	
17	Mumps[3]				☆
18	*Neisseria meningitidis* sero-group A[3]			☆	
19	PCV[2]	2011	☆		
20	Rabies[3]				☆
21	Rotavirus[2]	2013	☆		
22	Rubella[2]			☆	
23	Shingles vaccine[3]				☆
24	Typhoid[3]			☆	
25	Varicella[3]				☆
26	Yellow fever[3]	Planned	☆		

(Source: [a] MOH 2015, [b] Nosal 2011, [c] Loharika 2018) [1]Initial Vaccines [2]Universally Recommended Vaccines [3]Vaccines Recommended for Targeted Use

Table 3.2: Ethiopian expanded program on immunization vaccination schedule

Schedule	Visit Number	Antigen(s) Administered*
Birth	1	BCG, OPV0
6 weeks	2	PENTA1, OPV1, PCV1, Rota1
10 weeks	3	PENTA2, OPV2, PCV2, Rota 2
14 weeks	4	PENTA3, OPV3, PCV3, IPV
9 months	5	Measles
6-59 Months	6	Vitamin A supplement

*(Source: Masters et al 2018) *BCG: Baccilus Calmette-Guerin, OPV: Oral Polio Vaccine, PENTA: Pentavalent Vaccine (Diptheria-Pertussis-Tetanus, Hepatitis B, Haemophilus Influenzae type B), PCV: Pneumococcal Conjugate Vaccine, Rota: Rotavirus Vaccine, IPV: Inactivated Polio Vaccine.*

Key informant results suggest that coverage with routine immunization system has never been satisfactory. Reaching and maintaining high coverage level continues to be a challenge both at national and local levels, particularly in pastoral areas. Furthermore, this is compounded by high turn-over of staff at facilities within the public sector. Nevertheless, vaccination campaigns usually achieve very high coverage, indicating the fact that vaccine acceptance is still at favorable levels. Vaccine hesitancy and possibility of mistrust among the public has also been considered as an emerging threat to vaccine uptake and coverage. This is said to be largely due to fake news that is at present aggravated by the spread of unfounded and scientifically unproven information through social as well as mainstream local media outlets.

3.2 Vaccines not currently in use in Ethiopia

Vaccine for yellow fever, which has repeatedly been introduced from neighbouring countries, could be included in the routine immunization system (MOH 2015). Dengue fever has been recently detected in some parts of the country (Kitaw et al. 2017) and the introduction of the newly available vaccine (Lee et al. 2017) could be envisaged. "Strategic Advisory Group of Experts (SAGE) recommended that countries consider introduction of CYD-TDV [the dengue vaccine] only in geographic settings (national or subnational) with high endemicity, as indicated by seroprevalence of approximately 70% or greater in the age group targeted for vaccination or other suitable epidemiologic markers. The vaccine is not recommended where seroprevalence is below 50% in the targeted age group" (Turner 2016).

4. NEW GENERATION VACCINES

New vaccines are needed to reduce child mortality; prevent and control outbreaks; eliminate and eradicate vaccine-preventable diseases; and respond to rapidly increasing antimicrobial resistance. GAVI has, since 2010, added human papillomavirus (HPV), Japanese encephalitis, inactivated polio, and rubella vaccines to its portfolio, and some countries have licensed a dengue vaccine (R4D 2017).

New vaccine platform and delivery technologies that can have significant positive impacts on the effectiveness, acceptability, and safety of immunizations in developing countries are increasingly available. Identifying and prioritizing vaccines that will benefit most from enhanced technological attributes is among the critical issues to be tackled to bridge the gap between technology development and product development. In addition, incentives should be built for products with enhanced attributes, and resources as well as assistance should be provided to product development partnerships for adopting the enabling technologies (Chen & Zehrung 2013). According to the Gates Foundation, there are developments in creating new vaccines that are effective after a single dose, that can be delivered without needles, and that do not require refrigeration (Alcock 2010).

Although donor support for vaccine technology development is strong, the uptake of proven technologies by the vaccine industry and demand for them by purchasers continues to lag. There are challenges and opportunities associated with accelerating the availability of innovative and beneficial vaccine technologies to meet critical needs in resource-poor settings over the next decade. Progress will require increased dialogue between the public and private sectors around vaccine product attributes; establishment of specifications for vaccines that mirror programmatic needs; stronger encouragement of vaccine developers to consider novel technologies early in the product development process; and broader facilitation of research and access to technologies through the formation of centers of excellence. Progress also requires basing vaccine purchase decisions on immunization systems costs rather than price per dose; possible subsidization of early technology adoption costs for vaccine producers that take on the risks for new technologies of importance to the public sector; and provision of data to purchasers, better enabling them to make informed

decisions that take into account the value of specific product attributes (Kristensen & Chen 2013, Homma et al. 2013).

4.1 Vaccines on the horizon

"The future for vaccines is bright as new vaccines wield the ability to avert additional diseases; new delivery, formulation, and stabilization methods improve immunization effectiveness; and new sources of funding are secured to ensure that those in greatest need have access to these life-saving products" (Kristensen & Zaffran 2010). The WHO Initiative for Vaccine Research (IVR) established in 1999 has successfully promoted the development of various vaccines (WHO 2010) thus enabling targeted use of resources to respond to public health needs [United Nations Development Program (UNDP) 2016)]. The Vaccine Presentation and Packaging Advisory Group (VPPAG), which provides a unique forum for industry and public-sector dialogue on presentation and packaging of vaccine products, has recently completed a draft generic preferred product profile for new vaccines for developing countries (Kristensen & Zaffran 2010). Thus, a number of new vaccines could be available in the near future.

"At the same time, the development of vaccines and other immunization innovations is facing increasingly complex manufacturing and regulatory processes, as well as rising research, development and production costs" (WHO 2013). Indeed, vaccine introduction process is grounded in establishing a sound evidence base on the epidemiology and burden of the disease (including the distribution of serotypes or strains if relevant to vaccine policies) and the safety, efficacy and relative cost-effectiveness of the vaccine as a solution. In short, this process needs to reach a technical consensus that, based on the evidence, the vaccine is proven safe and effective for preventing the target disease (Levine 2010, Newall & Hutubessy 2014). Thus, in the short haul, "launches of highly efficacious vaccines for HIV, tuberculosis, or malaria would be unlikely" (Young et al. 2018, Kling et al. 2014, UNDP 2016, WHO 2018). The introduction of new vaccines (for example, against dengue and malaria) or underutilized vaccines (for example, those against cholera, human papillomavirus, rabies, rotavirus, rubella and typhoid) will require improved supply and logistic system; enhanced capacity and motivation of human resources; and increased and sustainable financing mechanisms (WHO 2013, Molina-Aguilera 2015).

4.1.1. Malaria vaccines

Protozoa such as plasmodia are more complex organisms than bacteria and viruses, with more complicated structures and life cycles; thus presenting problems in vaccine development. To help guide and channel global community and industry efforts towards the appropriate

products for optimal public health impact, WHO has defined research priorities and indicated target product profiles (TPPs) of medicines, vaccines and diagnostics for malaria and over 20 vaccines were in clinical trials or advanced pre-clinical development (UNDP 2016). In October 2015, two independent WHO advisory groups – the Strategic Advisory Group of Experts (SAGE) on Immunization and the Malaria Policy Advisory Committee (MPAC) – jointly called for pilot implementation of the vaccine in limited settings in sub-Saharan Africa. However, to date, the protection level (35%) has proved low (WHO 2018b) and the launching of pilot programs recently continues to fuel the controversy around low level of protection (Maxmen 2019).

4.1.2. TB vaccines

TB continues to be a major threat to human health worldwide with an estimated one-third of the world's population infected with *Mycobacterium tuberculosis*. Only 5-10% of the infected develop active disease with the remaining infected individuals developing latent infection constituting a large reservoir for potential reactivation to active disease and transmission. "Developing an effective TB vaccine is complicated by the lack of clear correlates of protection or immunity, the large expense of vaccine trials, and the diversity of human populations and environmental factors that may necessitate multiple vaccines" (Kling et al. 2014). Thus, even though there are several (at least 12 different antigen candidates) at varying levels of clinical trials, defining appropriate end points has proved difficult (Kling et al. 2014). With the growing threat of MDR TB and as new vaccines are not expected on the market before 2025 (UNDP 2016), "Continued support for the development of new TB vaccines should remain a priority as an effective vaccine would bring huge public health benefits" (Dockrell 2016).

4.1.3. Vaccines for STI/HIV

Vaccines against sexually transmitted infections (STIs) targeting young age groups has the potential to "catalyze a life course approach" to promoting and protecting sexual health. But, as seen for HPV vaccine, it is fraught with several challenges including the need for support with comprehensive and appropriate information, including on sexuality; and who grants consent for the intervention and on what basis (Kling 2010, Hawkes et al. 2014, Fesenfeld et al. 2013). Some countries have also introduced 'gender-neutral program' involving vaccination of boys (Green 2018).

Although a strategic objective of the Global Vaccine Action Plan (GVAP) is a vaccine with greater or equal to 75% efficacy for HIV/AIDS and large amounts of effort and finances are being invested, with good cooperation between public and private partners. This is

coordinated, in part, by the Global HIV Vaccine Enterprise (GHVE) developing an effective vaccine against HIV remains challenging (Maclennan 2013, Maclennan & Saul 2014, Loharikar et al. 2016, Pagliusi et al. 2016).

4.1.4. Vaccines for neglected tropical diseases

Ethiopia has one of the largest numbers of NTD cases in Africa with most of the more than 17 NTDs in the WHO list present, except for probably Chagas disease and yaws (Kitaw et al 2017). Development of vaccines for NTD has proved problematic mainly because these are not problems of high income countries and mobilizing the required resources has proved difficult as "New vaccines for which there is a need in high-income, as well as low-income countries, present a more attractive commercial incentive to the pharmaceutical industry than vaccines that will only be used in low-income countries" (Maclennan 2013). Therefore, the focus has been on treatment for those with effective and cheap treatment. There are no candidate vaccines for 2020 even for Leishmaniasis, which has second- and third generation vaccines based on recombinant proteins and deoxyribonucleic acid (DNA) constructs (UNDP 2016).

4.1.5. Novel Influenza Vaccines

Each year, a large proportion of people - 10–20% of Americans, for example - are infected with influenza, with the highest rates of complication occurring in the elderly population, and children (Kling et al. 2014). "Influenza virus mutates rapidly, enabling it to evade natural and vaccine-induced immunity. Furthermore, influenza viruses can cross from animals to humans, generating novel, potentially pandemic strains" (Pagliusi et al. 2016) causing seasonal outbreaks. Low-income countries suffer the most from these seasonal outbreaks. Recent events related to Ebola and Zinka viruses and the threats from avian/animal influenza are clear warning signs of species jumping with growing pandemic potentials with population growth and expansion and climatic changes. The need for preparedness for a potentially devastating pandemic such as the Spanish Flu/*Yehedar Beshta* is patent (Kitaw & Kaba 2018).

To meet such challenges, vaccine designs are evolving (Kling et al 2014). WHO's Global Action Plan for Influenza Vaccines (GAP), in collaboration with the United States Department of Health and Human Services has produced a checklist to support policy-makers and influenza vaccine manufacturers in identifying key technological, political, financial, and logistical issues affecting the sustainability of influenza vaccine production. The aim is to increase equitable access to pandemic vaccines while contributing to international pandemic preparedness efforts (Nannei et al. 2016). Current influenza vaccines only induce strain

specific response and may be ineffective against new influenza viruses. Several innovative influenza vaccine candidates, more potent, durable, and broadly protective than previously licensed vaccines are being developed and might be available in the foreseeable future (Rappuoli et al. 2011, Scorza et al. 2016, Pagliusi et al. 2016).

4.1.6. New formulations/better vaccines

For two important diseases, *Neisseria meningitidis* and *Streptococcus pneumoniae* with various and rapidly evolving sero-groups, there is a challenge of providing effective vaccines. For example, repeated formulations with increased number of serotypes have shown the highly adaptive nature of pneumococci. "Epidemiologic evaluations of pneumococcal nasopharyngeal (NP) colonization, Invasive Pneumonia Disease (IPD), and acute otitis media (AOM) already suggest an insufficient solution with PCVs because new types being added will not prevent infections by the many emerging serotypes expressed by pneumococci … [Raising the question of] Where and when do we end with newer PCVs?" (Pichichero 2017). Therefore, the solution seems to lie in the next-generation of multicomponent whole-cell vaccines (WCV) or purified protein vaccines.

4.2 Issues of introducing new vaccines in Ethiopia

A number of problems with introduced vaccines/vaccine effectiveness in developing countries should be addressed. Studies have shown that some vaccines, those administered orally in particular show much lower effectiveness in Low-Middle Income Country (LMIC) than in HIC (McQuestion et al 2011). Thus, rotavirus vaccine, which works in 98 percent of the children who receive it in wealthy countries such as the United States and Finland only protected 39% in sub-Saharan Africa, 43% in rural Bangladesh, and 58% in Nicaragua. The same has been observed for oral polio vaccine (Storrs 2016). While this differences in effectiveness among developed and developing settings are attributable to various determinants, antigenic variation between locally prevalent viral strains and the strains in vaccines produced overseas may pose an important challenge requiring due attention.

Background data on economic burden and characterization of circulating strains for a specific disease is required to hasten the introduction of a given antigen for intervention (Aminu et al. 2010). In the case of Rubella, conducting sero-prevalence studies among child bearing age females and establishing congenital rubella syndrome sentinel surveillance among young infants are critical to better understand the magnitude rubella prior to vaccine introduction (Getahun et al. 2016). Iimmunization programs in developing countries in general are experiencing a number of practical, logistical, and safety concerns as new vaccine products are being introduced. Most programs do not have the cold chain storage

capacity to handle increasing volumes. New vaccines often target different age groups than the traditional course of vaccines for infants and require new delivery strategies. New product handling instructions, changes to vaccine storage recommendations designed to reach populations living beyond the reach of the existing cold chain infrastructure etc. tend to overwhelm already under resourced systems. Predictably, "…new vaccine-delivery methods such as jet injectors, micro-needle patches, dissolvable tablets, sublingual gels, and nasal drops or sprays will become more available" (Kristensen & Zaffran 2010). The vaccine supply chain needs to be integrated with other public health supplies, re-designed for efficiency and effectiveness and work is needed, in the longer term, to eliminate the need for refrigeration in the supply chain (Lloyd & Cheyne 2017). "The bottom line is that in the future the handling, management, and use of vaccines will become increasingly complex" (Kristensen & Zaffran 2010).

"Even as the polio eradication initiative redoubles its efforts to achieve regional certification in 2017, Africa needs to plan early for the eventual ramp down of Global Polio Eradication Initiative (GPEI) support. GPEI support for polio-funded resources will gradually reduce over the next three years, as regional and global certification of polio eradication draws closer. In preparation for this ramp down, national governments, donors, implementing partners and civil society must work together to plan for a successful transition" (Mihigo et al. 2016). Transition plans will require dialogue with broad health systems planners and address country management of logistics and supply need; plan and budget for future new vaccines; focus on domestic resource mobilization; and ensure sustainability and capacity of institutions (Loharikar 2018).

Reflecting global trends, NCDs are on the rise in Ethiopia but infectious diseases remain major challenges with high burden of diseases and mortality [Kitaw et al. 2017, Federal Democratic Republic of Ethiopia (FDRE) 2015, MOH 2015 and 2015a)]. Historically and currently, vaccines remain highly acceptable interventions in the country (Larson et al. 2016) with strong support both in the Health Policy (FDRE 2015) and the Health Sector Transformation Plan (HSTP) (MOH 2015). However, there is no place for complacency as experiences elsewhere show, years of confidence building could be easily undone (Sadanand 2011, Larson et al. 2016, Caplan & Hotez 2018). The Human Resources for Health (HRH) base in Ethiopia is very limited and suffers from important challenges of quality, motivation/retention and equitable distribution (Kitaw et al. 2014, MOH 2015, Rueda-Torres et al. 2015). Immunization financing is highly donor dependent and its sustainability questionable if, as indicated in the development plans, the country is 'promoted/graduates' to MIC (MOH 2015a). Given the growth in the number of MICs and their considerable domestic income

disparities, they are now home to the greatest proportion of the world's poor, having more inhabitants below the poverty line than low-income countries (LICs). However, they have little or no access to external funding for the implementation of new vaccines, nor are they benefiting from an enabling global environment (Kaddar et al. 2013, Berkley 2019).

5. CHALLENGES OF INTRODUCING NEW VACCINES IN LOW-MIDDLE-INCOME COUNTRIES

"There is no perfect method to predict a new vaccine introduction and to determine vaccine demand." (Mogasale et al. 2017). However, these could be fine-tuned through economic evaluation of vaccination, which is a key tool to inform effective spending on vaccines. In addition, in order to capture features of vaccines which are relevant to decision makers, broader societal benefits (such as improved educational achievement, economic growth and political stability), reduced health disparities, medical innovation, reduced hospital beds pressures, greater peace of mind and synergies in economic benefits with non-vaccine interventions should be assessed. The fiscal implications of vaccination programs should also be made explicit (Kaddar et al. 2013, Jit and Hutubessy 2016).

5.1 Socio-economic/financial challenges

Vaccine acceptance is influenced by a complex relationship among factors that drive individual decision-making behavior, and socio-cultural and political contexts, including the rapid proliferation of information technology, which could "opened the gates for the viral spread of panic, such as around HPV vaccine risks (Larson 2018). The decision to receive a vaccine is, in turn, based upon a dynamic assessment of the risks associated with vaccination vs. the risk of not being vaccinated, i.e., the risk-benefit ratio. This risk-benefit assessment is greatly influenced by socio-cultural and political contexts that drive health beliefs, economic priorities and ones relationship with the health care system (Feemster 2013).

For a number of reasons - the uncertainty in the total benefit (direct and indirect) to be measured in a population when using a cohort model; issues of appropriate rules about discounting the long-term impact of vaccines; differing and opposite contexts in low-income and high-income countries -performing a total health economic analysis of a vaccine newly introduced into the market today. These include using the conventional cost-effectiveness analysis normally applied on pharmaceutical products, is a challenge. Thus, "the approach, as compared with the introduction of a new drug in the treatment arsenal, should at least cover the full societal impact beyond health-care costs only and ideally consider additional parameters that concern various stakeholders in the decision-making process such as the

various ministries involved and individual health-care providers including hospital managers" (Postma & Standaert 2013).

Table 5.1: Percentage (%) of vaccine cost and RI cost funded by Government 2015

Country	% of vaccine cost	% of RI cost
South Africa	100[1]	100
Swaziland	50-91[2]	50-92
Ethiopia	14	39
Kenya	10	Missing
Central African Republic	2	1

Source: Mihigo et al 2017) [1]+4 others, [2]+5 others

Countries face numerous challenges in the introduction of new vaccines. Foremost among them is consistent and predictable financing of the new vaccines, and the costs associated with expanding the immunization system (MOH 2015). Most national immunization programs in developing countries (Table 5.1 for examples from Africa) are financially and organizationally weak at national and local levels in part because they depend heavily on funding from foreign sources (McQuestion et al. 2011). Countries need to lessen their dependency on external partners in order to build technical and organizational capacity in their health sectors. Specific pathways to sustainable immunization financing, particularly through advocacy to strengthening immunization programs through budget reforms, decentralization, legislation and innovations, are recommended (Athrly et al. 2012, McQuestion et al 2011, SIV 2019). Vaccines could be expensive as manufacturers charge much higher than manufacturing costs e.g. 7 to 9 times higher for HP vaccines (Clendinen et al. 2016).

A key challenge will be mobilizing the resources to finance non-vaccine immunization components in each country. Securing funds to cover non-vaccine costs has always been more difficult than getting national or international funding to pay for the vaccines (Le Gargasson et al. 2015). According to projections of future financial flows for vaccination form 2011 to 2020, 65% of the need for routine vaccination will not be met. Strategies to fill the expected funding gaps are all the more pressing because of the impact that front-loading investments in earlier years would exert on countries' readiness to introduce new vaccines and because achieving certain infrastructural improvements can take several years. EPI's continued success and the health and economic benefits that immunization will confer during the decade from 2011 to 2020 will hinge on sufficient financing of the non-

vaccine components of routine vaccination services. Failing to mobilize adequate resources to finance these critical program components will seriously compromise the ability of low and lower-middle income countries to meet the targets of this decade's Global Vaccine Action Plan (Lydon et al, 2014).

Key informant responses suggest that finance is among the major challenges anticipated in the drive to introduce new vaccines in Ethiopia. As in many developing settings, the immunization program is basically donor dependent, and government's role in financing the program is said to be minimal with little or insignificant contribution from the private sector. As mentioned above, issues of financing and sustainability are the major points raised by all the key informants. The immunization program is largely donor dependent and there seems to be donor fatigue. The government is said to be facing the challenge of shouldering all the costs related to vaccination soon after graduation from GAVI support. Key informants said that the government needs to consider alternative financing approaches as well as plan for local or regional production of vaccines to help alleviate the emerging financial constraints.

The financial sustainability of new vaccine introduction remains a challenge in the face of a fiscal crisis, where new vaccines have to compete with other health system priorities, even if the vaccine being considered for introduction is expected to contribute to the reduction of the morbidity and mortality of a public health problem. The introduction of new and underutilized vaccines in a developing country requires wide-reaching analyses of technical, political and programmatic aspects for decision-making. The economic criterion is essential for decision-making given the high costs of new vaccines. Evidence generation through studies of cost-effectiveness and financial analyses that contribute to introduction sustainability are, therefore, required (Molina-Aguilera 2015, Howard et al. 2017).

Another challenge is 'vaccine hesitancy i.e. delay in acceptance or refusal of vaccines (Turner 2016) ranging from fears that vaccines are being used for sterilization or even infection to misuse of funds (Larson et al 2016). In Ethiopia, as suggested by the key informant interview results, the challenges also include those related to acceptance in view of fake news, different cultural beliefs, and fatigue of too many injections. Some of these are not unfounded as even seemingly legitimate vaccination programs have had ulterior motives. There will never be a completely risk-free vaccine, but problems can be minimized through more coordinated surveillance efforts, ensuring the accountability of vaccination programs administered by outside groups, improved dialogue about the importance and mechanism of vaccines, and programs tailored to address the concerns of the local population" (Sadanand 2011, Caplan and Hotez 2018).

5.2 'Health system' challenges

The challenges faced by developing countries in their efforts to introduce new vaccines include competing priorities, lack of enough data on cost-effectiveness and lack of surveillance systems to support new vaccine introduction (Chauke-Moagia and Mumbab 2012, Mihigo et al. 2017). Need for additional costs for staff training, distribution of vaccines and logistics and social mobilization activities hamper progress to achieve high immunization coverage in developing settings. Countries must also incorporate their vaccine introduction plans into donor-required assessments and multi-year plans. However, there seems to be limited experience with such proactive planning process in low-income countries highlighting the importance of integrating the planning processes for new vaccine introduction into broader immunization systems planning and financing (WHO 2013 & 2018b, Gordon, 2012, Wang et al. 2013). There is also an urgent need for more global consensus and a tightly coordinated, comprehensive and compassionate approach to vaccine introduction. Vaccine-preventable diseases do not respect political borders (Kochhar & Seeber 2013).

The key to success of introducing a new vaccine in a developing country is the modality used in integrating it with other intervention programs of the country. The program should interact synergistically with other interventions, but this synergy needs to be documented in a variety of situations where the vaccine will be used. Mechanisms of the synergy include both biological and logistic synergy. Biologically, the vaccine may induce herd protection by reducing the environmental contamination of the pathogen making other intervention program activities more effective. In turn, the other interventions reduce the inoculum that potential patients consume and this increases the effectiveness of the vaccine. Further activities include the functions of policy advice, process guidance, quantitative assessment and experience sharing and planning. The need to make important decisions about the use of new vaccines provides an excellent opportunity for countries to consider the use of broader advisory committees to deliberate and address strategic issues and health priorities at national level. These activities are important for a developing country for introducing a new vaccine, though they should be carefully tailored to meet the different needs of the individual country (Kochhar & Seeber 2013). Experience and research have shown vaccine strategies that work well and the factors that encourage success, often including strong support from government and healthcare organizations, and tailored and culturally appropriate approaches. There is no one-size-fits-all solution and vaccine strategies have to be adapted according to local conditions (Hardt et al. 2016).

The health/vaccine delivery system in Ethiopia exhibits several weaknesses, including concerns with quality[5] (Box 5.1). The key informant results particularly highlight health system challenges to include low staff motivation, high turn-over of staff, as well as overload, lack of ownership by the community due to poor social mobilization, lack of skills on refrigerator preventive maintenance, and poor recording and documentation system. The results also emphasize sparse settlements and pastoral way of residence have are crucially important in this regard.

Box 5.1: Weaknesses in vaccine delivery system in Ethiopia:

- Sub-optimal quality of service
- Limited integration of EPI and other maternal and childhood interventions
- Inadequacy in continuum of care
- Lack of availing all services to clients at every encounter
- Low effective vaccine coverage
- Inequity/avoidable inequalities
- Limited access to health facilities in developing regional states in particular
- Disparity in vaccine coverage among regions, zones, woredas, urban and rural areas
- Shortage of adequately trained EPI service providers and EPI managers
- Poor utilization of services; service irregularity and interruption
- Weak feedback/ information/communication system
- Limited community/user awareness

Source: Tadesse et al 2017, Kitaw et al 2017, MoH 2015)\

New vaccine introduction and immunization strategies (including vaccine transition in the country) could help in improving the countries health system infrastructure, and enhance disease surveillance (Kochhar & Seeber 2013). According to a case study that included Ethiopia (Burchett et al. 2014), the introduction of new vaccines is said to have both positive and negative effects on the health systems, even though these were reported to be temporary, around the time of introduction. The positive effects include enhanced credibility of the immunization program and strengthened health workers' skills through training. Negative effects included an increase in workload and stock-outs of the new vaccines.

Additions of increasing number of new vaccines have raised concerns of overburdening EPI and the health system in general. Studies indicate that there are almost no negative impacts for vaccines that fit into routine schedules. "New vaccine introduction was most efficient when the vaccine was introduced into an existing delivery platform and when introduced in combination with a vaccine already in the routine childhood immunization schedule (i.e., as a combination vaccine)" (Hyde et al. 2012). In fact, there could be some (short-term) positive effects on introducing new technologies (auto-disable syringes for example), improved staff skills, improved social mobilization and the availability of financial resources (Hyde et al. 2012, Torres-Rueda et al. 2015).

5 Poor quality "was an important driver of 81% amenable mortality [from] vaccine preventable diseases" (Kurk et al 2018).

A major issue is sustained vaccine provision. Reportedly, "Every year on average, one in every three WHO Member States experiences at least one stock out of at least one vaccine for at least one month" (Lydon et al. 2017). As would be expected, the incidence is most pronounced in Sub-Saharan Africa with 38% of countries reporting national-level stock outs mostly (80%) due to internal[6] reasons including government funding delays (39%), delays in the procurement processes (23%), and poor forecasting and stock management (18%) (Lydon et al. 2017).

In spite of laudable efforts in recent years (Belete et al. 2015, MOH 2015. Kitaw et al 2017), "Ethiopia suffers from some of the lowest vaccination rates on the continent, leading to an unnecessarily high burden of potentially preventable diseases" (Masters et al. 2018). Only about 50% of one-year-olds in Ethiopia were covered by DTP3 immunization and except for gender, there were high inequalities[7] in distribution by education level, household income, urban residence and certain subnational regions [especially Addis Ababa, Dire Dawa and Tigray, where coverage was over 80%] (WHO 2018, see also Fig 1.3).

In terms of HRH, the majority of immunization service is being rendered by the HEWs recruited from the lowest administrative unit, the Kebele. HEW suffer from major weaknesses including inadequate system for retention leading to high attrition rate; inadequate upgrading/career system; inequitable distribution of skilled human resource; low provider motivation; inadequate mechanisms for improving capacities of immunization program management; and weak knowledge management at all levels (Kitaw et al. 2014, MOH 2015, Rueda-Torres et al. 2015).

6 Also recent supply shortages of rotavirus, PCV, IPV and HPV vaccines due to: a) Vaccine markets and limited numbers of manufacturers; and b) increasing demand and inaccurate supply forecasting (Loharikar 2018)

7 **Inequity in vaccine delivery within countries is associated with:** •Conflicts, fragile situations, or humanitarian emergencies; •Residence (urban or rural), with low coverage in urban slums and remote rural communities; •Nomadic populations and ethnic minorities; •Economic status (wealth quintiles); •Education (of mothers); •Gender; •Vaccine hesitancy (Loharikar 2018)

6. POTENTIAL OPPORTUNITIES AND LESSONS TO BE LEVERAGED

After the endorsement by global health leaders of the Decade of Vaccines (2011–2020), a Global Vaccine Action Plan (GVAP) was endorsed in May 2012 by Ministers of Health from 194 countries. However, a midterm review showed most commitments were not met (Table 6.1).

Table 6.1: Global Vaccine Action Plan (GVAP Mid-point Progress Targets 2015)*

Not Achieved	Achieved
1. DTP3: All countries >90% national coverage, and >80% in every district by end 2015 2. Polio: transmission stopped by end 2014 3. Maternal and neonatal tetanus: eliminated by 2015 *[achieved in 2017, WHO 2018 a&b]* 4. Measles: eliminated in 4 regions by end-2015 5. Rubella: eliminated in 2 regions by end-2015	Introduction of new and under-utilized vaccines: At least 90 low-or middle-income countries to have introduced one or more such vaccines by 2015

* *Source: Adapted from Loharikar 2018*

The Ministers of Health also agreed on a Vaccine Procurement Baseline (VPB) proposal requiring all countries to spend a minimum of 0.01% of Gross Domestic Product (GDP) on vaccine procurement. If recommended vaccines could not be obtained with those funds, the balance would be paid by external sources. There have been calls to make Vaccine Procurement Assistance (VPA) a clearly defined and specific subcategory of Official Development Assistance (ODA) and that all donor governments commit to allocating more than 0.02% of GDP for vaccine procurement for recipient countries and also raise VPA to 0.02% of GDP, the monitoring of which could be a strong advocacy tool (Nelson et al. 2014). In 2016, African Ministers of Health, Finance, Education, Social Affairs, Local Governments and parliamentarians (Mihigo et al. 2016) issued a ***DECLARATION ON "Universal Access to Immunization as a Cornerstone for Health and Development in Africa",*** the Addis Declaration on Immunization (ADI), endorsed by all Heads of States on January 31, 2017. Thus, they committed themselves to continued investment in immunization programs and a healthy future for all people of the African continent (Box 5.1). "The event also

brought together advocates, technical experts, policymakers, partner agencies, donors and journalists to examine how best to drive forward immunization across Africa" (Mihigo et al 2016). The ensuing ADI roadmap outlines three strategies: 1. Generate and sustain political commitment and funding for immunization through advocacy and communications; 2. Address gaps in immunization and work with key partners to overcome barriers to access and utilization of immunization services, 3. Monitor progress to drive impact and ensure accountability (WHO AFRO 2017).

Box 6.1: DECLARATION ON "Universal Access to Immunization as a Cornerstone for Health and Development in Africa"

We, African Ministers of Health, Finance, Education, Social Affairs, Local Governments attending the Ministerial Conference on Immunization in Africa, **hereby collectively and individually commit ourselves to:**

- Keeping universal access to immunization at the forefront of our efforts to reduce child mortality, morbidity and disability …
- Increasing and sustaining our domestic investments and funding allocations …

March 2016, Addis Ababa

Most of the new vaccines, especially those introduced in Ethiopia - HepB) vaccine, Hib vaccine, PCV, and rotavirus vaccine - were incorporated in the routine childhood immunization schedule and therefore presented only limited challenges (Rueda-Torres et al. 2015, Molla et al 2015, Olayinka et al. 2017). Other new vaccines, such as human papillomavirus (HPV) vaccine, meningococcal vaccine, yellow fever vaccine, and typhoid vaccine that are intended for older or at-risk population could be more challenging both on the immunization system and the broader health system (Hyde et al. 2012, Glatman-Freedman et al. 2010, Gallagher et al. 2017).

6.1 Socio-economic/financial opportunities

Immunization, through EPI in particular, has major impact on global health and economy. This has been boosted by support from the Global Alliance for Vaccines and Immunization (GAVI), which was established in 2000 as a public-private partnership with a mission to improve global health through increased access to vaccines in low-income countries (Maclennan and Saul 2014). GAVI provided essential support for an unprecedented increase in the use of (HepB) and Hib containing vaccines in resource poor countries. This increase was supported with significant funding from international donors, intended to be time-limited (Zuber 2011). GAVI "has disbursed at least US$6 billion during 2000-2016 for vaccine introductions and health system strengthening activities in 37 African Region countries" (Casey et al. 2017).

Support from philanthropists such as "The Bill and Melinda Gates Foundation (BMGF) which pledged US$10 billion to support the research, development and delivery of vaccines for the poorest countries in a New Decade of Vaccines" (Maclennan 2013) have played significant role. Collaboration between these and WHO and UNICEF has meant that more new vaccines are introduced more rapidly (Loharikar et al 2016). "The February 2016 Addis Declaration on Immunization in which African heads of state committed to increasing domestic resources for immunization and improving the effectiveness and efficiency of immunization programs is a sign that the necessary political commitment exists ... The fulfillment of the pledges in the declaration will be essential to maximizing the benefits from immunization in the African Region" (Casey et al. 2017).

However, in spite of successes to date, infectious diseases remain major health challenges in LIC in particular. Thus, the risk of dying from infectious diseases is 15-fold higher in LMIC as compared to HIC while that from NCD is the same (Maclennan & Saul 2014). "There is an urgent need for more reliable national ownership of immunization programs with commitment for guaranteed funding of all aspects of immunization in the Region" (Mihigo et al. 2016, see also SVI 2019).

6.2 'Health system' opportunities

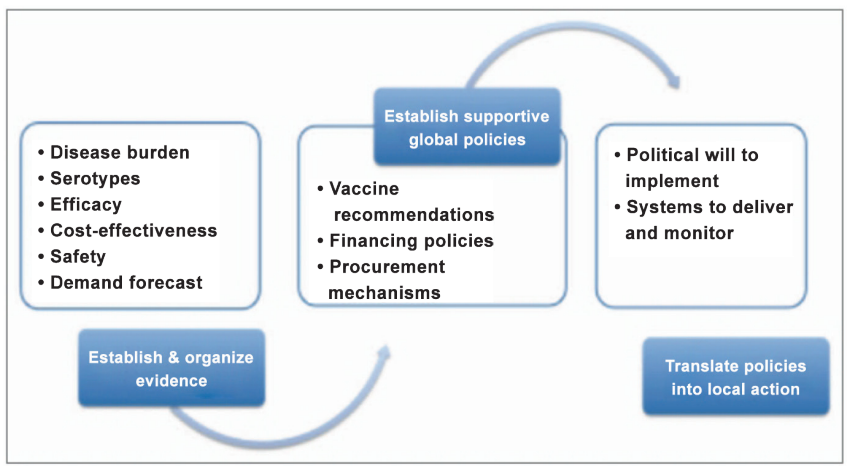
Improved cross-fertilization of knowledge between industry and academia, and between human and veterinary vaccine developers are said to lead to more rapid application of promising approaches and technologies in the development of vaccines. In addition, identification of best-practices and development of checklists for product development plans and implementation programs are seen as low-cost opportunities to shorten the timeline for introduction of new vaccines and technologies (Bregu et al. 2011).

A review of the current status of scientific and technical progress in the development of vaccines for neglected tropical diseases also highlights the contributions being made by non-profit product development partnerships that are working to overcome some of the economic challenges in vaccine manufacture, clinical testing, and global access (Bethony et al. 2011). Similarly, resources made available to countries through the Global Alliance for Vaccine Initiative (GAVI) has facilitated the implementation of crucial activities in the introduction of certain vaccines within a short timeframe (Blankenhorn et al. 2017). Nevertheless, despite the huge advances already achieved, costs of prevention and medical care, the implementation of what is technically possible, socio-political resistance to prevention opportunities, the very wide ranges of national economic capabilities, and health care systems pose challenges to the development and introduction of vaccines in

developing countries, requiring significant efforts in international advocacy (Bosch et al. 2013).

Based on experience with accelerating the adoption of Hib, pneumococcal and rotavirus vaccines and an existing set of WHO guidelines for new vaccine introduction, a policy framework is proposed for considering the issues and challenges to accelerating new vaccine adoption. The framework organizes the major steps in the process into a continuum from evidence to policy through implementation, and finally access (Fig. 6.1). The authors acknowledge the fact that this process is multi-disciplinary and involves multiple stakeholders including epidemiologists, vaccine scientists, economists, clinicians, behavioral scientists, advocates, policy analysts, communications specialists, politicians, health workers, communities, vaccine manufacturers, international agencies, donors and more (Levine 2010).

Fig 6.1: Evidence to policy to implementation *(Source: Levine 2010)*



In LICs, there are several areas where concerted efforts are necessary in prioritizing new vaccines to successfully introduce them into immunization programs. First, the prioritization of new vaccines should be based on explicit frameworks. There is a need for enforcement mechanisms to ensure that vaccines identified as a priority are not overtaken by vaccines that are not considered to be a top priority. This requires the direct involvement of key stakeholders such as district officers in determining national level priorities. The process should also require public consultations and involvement. This would call for raising public awareness about the priority setting process and the rationale behind the decisions. Monitoring implementation of the new vaccines should also involve monitoring the public

response to the set priorities and their implementation. The existing power imbalances between sub-national governments, national governments and their development assistance partners need to be mitigated by strengthening institutional capacity and leadership; this is essential to ensure that priorities are identified and implemented through an inclusive, transparent, and efficient process (Gonzalez-Lorenzo et al. 2017, Wallace & Kapirir 2015).

7. PROSPECTS OF VACCINE PRODUCTION IN DEVELOPING COUNTRIES

GAVI has significantly helped introduction of new vaccines in Africa but its sustainability is questionable, and new vaccines introduction post-graduation has been rare. Local vaccine manufacturing within Africa has several foreseeable benefits, including decreased cost and increased availability and the capability to provide vaccines to the region (Makenga et al 2019). The local manufacturing process can also spur economic growth. However, there are particular challenges involved in vaccine production, including process development, process maintenance, lead time, production facilities, equipment, life cycle management, and product portfolio management (Plotkin 2017). Some of the critical challenges and pitfalls are shown in Box 7.1 (Tekki et al., Walwyn et al). Vaccine manufacturing in Ethiopia will need an in depth study on its own.

Box 7.1: Prospects of Vaccine Production in Developing Countries

Pros

- Stable supply and sustainability
- Can be tailored to fit local genetic make-up
- Long-run self-sufficiency
- Local production can conscientize utilization of vaccines
- Adds up to local economy in industry, jobs, easing foreign exchange pressure
- Potential capability for regional level marketing

Cons

- Low willingness to pay due to lack of awareness and poverty
- Challenges of not having technological capacity
- High cost of development and production
- Challenges with provision of constant electric power - for industrial scale production, handling, transport and storage
- Diseconomy of scale in that demand and vaccine markets are low
- High requirements for regulatory capacity

Source: Tekki IS, et al., Walwyn DR. et al.

8. NEW VACCINE INTRODUCTION MODALITIES

Aspects deemed most important for new vaccine adoption are WHO recommendations, the existence of local epidemiological data (local burden of disease data), and a set of factors comprising affordability, cost-effectiveness, which provides a useful and comprehensible reference point, the cost implications of adopting a new vaccine, and overall cost of the new vaccine for the program (Makinen et al. 2012, Horton et al. 2017). Vaccine effectiveness needs to be defined in the context of low-resource settings. The strategy should move from 'number of lives saved at the end of the day' toward the 'prevention of suffering/disease burden'. New epidemiological models may be warranted to measure and adequately describe the real-world impact of vaccines (Kochhar & Seeber, 2013).

Strong and independent advisory mechanisms at the national level (e.g., National Immunization Technical Advisory Groups/NITAGs) are critical to ensuring informed and evidence-based recommendations about the introduction and financial sustainability of vaccines as countries face several opportunities and challenges (Ba-Nguz 2014, Bell et al. 2019). They could be considered as indicators of a country's commitment to immunization since the Global Vaccine Action Plan 2011–2020 (WHO 2013) called all countries to establish or have access to NITAGs by 2020. These should be interdisciplinary and multinational and could include representatives of MOH of (higher) education, Ministry of Finance, health professional associations, public health experts, private public partnerships with experiences in vaccination, clinical researchers, safety pharmacovigilance experts, WHO and other global partners (UNICEF, GAVI, Gates), and possibly funders and religious leaders (Kochhar and Seeber et al. 2013, Ba-Nguz 2014, Loharikar et al. 2016, Howard et al. 2018). Such bodies, for example WHO and the Supporting Independent Immunization and Vaccine Advisory Committees (SIVAC) Initiative supported functioning NITAGs, serve to counteract reliance on donor-driven decisions by facilitating systematic and transparent country-owned processes for developing immunization policies (Mantel and Wang 2012).

NITAGs support national policy-makers and program managers adopt evidence-based and locally relevant immunization policy and program decisions for all vaccines, across all populations. They could also provide credibility, raise public immunization awareness, engage with healthcare professionals, monitor program impact and act as referee or

technical resource in response to rumors or hesitancy (SAGE 2017, Howard et al 2018). To achieve these, they should be independent, transparent and use standardized and systematic approaches in decision-making process (Ba-Nzug 2014, Ricciardi et al 2015).

8.1 International/Regional/Country experiences

To support its "mandate to provide leadership on global policies, standards and norms and to support member countries in applying these to national programs to improve health", WHO has established or supported the establishment of advisory bodies at various levels (Table 8.1). More recently, a NITAG Resource Center (NRC) which fosters interaction between NITAGs and "offers NITAG members and secretariats a centralized access to NITAG recommendations from around the world, systematic reviews, scientific publications, technical reports, updates from partners, and upcoming immunization events." (Adjagba et al 2015) has been established. In May 2016, an international NITAG meeting called for the establishment of a global NITAG network (GNN) to strengthen NITAGs and their evaluation (SAGE 2017).

Table 8.1: WHO Immunization Policy Framework and Decision-making on Vaccine Introduction*

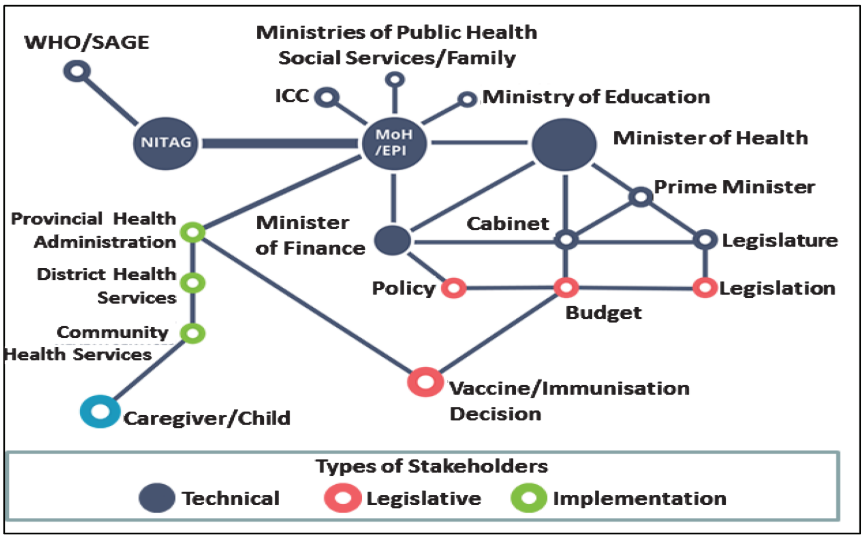
Level	Name	Function
Global	SAGE	Global policy recommendations
Regional	RITAG	Identifies regional priorities
		Sets regional policies & strategies
National	NITAG	Makes policy recommendations to national health authorities

** Source: Loharikar 2018*

The Strategic Advisory Group of Experts (on immunization) (SAGE), established in 1999, had some 15 independent experts that meet twice a year to develop evidence-based recommendations on global vaccine policies and strategies for vaccine-preventable diseases. These serve as the basis for WHO vaccine position papers, which inform country-level decision-making and program implementation and also those of partner organizations including the GAVI Alliance, non-profit organizations, and international professional associations.

The oldest NITAGs were established in the early 1960s – United Kingdom 1963 and USA and Canada 1964 - and by 2010, 89 of 187 responding countries had one with the lowest 11/34 in Africa (Bryson et al. 2010). As more new and improved vaccines become available, decisions on which to adopt into routine programs become more frequent and complex (Fig 8.1) and countries and NITAGs have to adapt to this complexity.

Fig 8.1: New Vaccine Context: Understanding Complex Decision-Making



The WHO's Epidemic Vaccine for Africa (EVA) project may be taken as good experience on what it takes to introduce a new vaccine in the African context. The project has served as an organizational framework for expert and partnership consultations for recommending the development and introduction of the group A meningococcal conjugate vaccine into the African meningitis belt (Aguado 2015). The experience of ***Burkina Faso*** (Box 8.1) shows that African national immunization programs are capable of achieving very high coverage for a vaccine desired by the public, introduced in a well-organized campaign, and supported at the highest political level.

Box 8.1: Burkina Faso's Experience Managing Vaccine Introduction Challenges

- Doing a large safety study and registering the new vaccine in the country
- Developing a comprehensive communication plan
- Strengthening the surveillance system with particular attention to improving the capacity for real-time polymerase chain reaction (PCR) testing of spinal fluid specimens
- Improving cold chain capacity and waste disposal
- Developing and funding a sound campaign strategy
- Ensuring effective collaboration across all partners

Source: Djingarey et al. 2012

The example of Bangladesh: In Bangladesh, the burden of disease, findings of research on vaccine-preventable diseases, political issues relating to outbreaks of certain diseases, initiatives of international and local stakeholders, pressure from the development partners, GAVI's support, and financial matters are the key factors in the introduction of new vaccines. To expedite the introduction and uptake of new vaccines, the study indicates that it is important that GAVI takes rapid action on the application for its support and the Government takes less time to complete the administrative work (Uddin et al. 2013).

The example of South Africa: South Africa has played a leadership role in the African continent with introduction of new vaccines, which dates back to 1995 with the introduction of hepatitis B, followed by the *Haemophilus influenzae* type b in 1999 and recently the national roll out of the pneumococcal conjugate and rotavirus vaccines in 2009.

South Africa has a functional decision making process for the introduction of new vaccines; with an established NITAG, referred to as National Advisory Group on Immunization (NAGI). NAGI has the responsibility to deliberate on key policy issues as part of the process for decision making on the introduction of new vaccines (Ngcobo & Cameron 2012). In developing recommendations, NAGI considers: disease burden, cost effectiveness, and the impact on the EPI. Although guidance and recommendations from WHO are considered, the decision to introduce a new vaccine in South Africa is based on local data. NAGI recommendations are presented to the National Department of Health (NDOH). The NDOH pursues the matter further through the involvement of provinces. When an agreement has been reached to accept the NAGI recommendations, the NDOH seeks funding from the Ministry of Finance (MOF). Once funds are available, the new vaccines are implemented by the immunization program.

Although there is an established functional system for decision making in South Africa, some areas need to be addressed. A system should be developed to allow the NDOH, NAGI and the MOF to engage in the deliberations on financial and economic impact of new vaccines. It is further recommended that ***a committee*** be established that will assess the programmatic issues to weigh the potential benefits of a new vaccine. Furthermore, ***political commitment*** should support the immunization program and strengthen it so that it can make an impact in the achievement of set targets (Ngcobo & Cameron 2012, Hotez 2016).

8.2 Ethiopian experiences

The process of decision making to adopt new vaccines is, by nature, political. In Ethiopia, as for many other GAVI-eligible countries, the main driver in recent introductions seemed to be seizing GAVI windows of opportunity for funding. Other drivers included political prioritization of vaccination or the vaccine-preventable disease and the burden of disease. "One of the greatest challenges for the future consists in finding a fair match between ever-increasing medical needs and possibilities on the one hand and finite health care budgets on the other hand. Consensus exists that such priority setting should reflect a concern for both efficiency, (making maximal use of valuable resources) and equity (avoiding that some people become deprived of their deserved share)" (Luyten et al. 2015). For Example, a 2014

study conducted to determine the prevalence and epidemiology of meningococcal carriage in Ethiopia prior to the introduction of meningococcal conjugate vaccine identified the presence of epidemic strains of sero-groups W and X, highlighting the need for multivalent conjugate vaccines covering these sero-groups (Bårnes et al. 2016). Decisions to introduce new vaccines (e.g. PC and rota) were essentially taken by the MOH with consultation in ICC as discussion forums and limited involvement of other stakeholders; even the Ministry of Finance which had to guarantee the GAVI co-financing (Burchett et al 2012, Molla et al 2015).

The E-NITAG was established, by MOH, only in May 2016 with seven core members essentially from the academia (Table 8.2). It was considering including additional experts such as health economists, pharmacologists, vaccine experts.

Table 8.2: Members of The Ethiopian National Immunization Advisory Group by Qualification (2016 and 2017)

Qualification	Number	
	2016	2017
Epidemiologist	1	1
MNCH Expert	1	-
Pediatrician and Infectious Disease Specialist	2	2
Pediatrician and Neonatologist	1	1
Public Health Expert	2	1
Gynecology & Obstetrics Specialist	-	1
Immunologist	-	1
Physician/Vaccine Expert	-	2
EPI Expert (Secretariat/MoH)	-	2

E-NITAG defined its **scope of action** (quoting WHO 2013) as "cover[ing] all issues relating to vaccination concerning all populations". Its major functions and responsibilities included:

- Conduct policy analysis and advise the MOH on national immunization policy.
- Guide the government of Ethiopia and the national immunization program (NIP) on the formulation of short and long-term strategies for the control of vaccine preventable diseases through immunization.
- Advise the national authorities in the monitoring and evaluation of the national immunization program and provide recommendations on the continuation or

modification of existing programmatic activities.

- Identify the need for further data for policy-making and advise the government in gathering relevant data.
- Provide the national authorities and the immunization program on the latest scientific developments in the area of vaccines and vaccine-preventable diseases (E-NITAG 2017).

E-NITAG is considered functional, meeting all WHO Joint Reporting Forms indicators in 2017 (Table 8.3). However, it will, as most newly established NITAGs, require strengthening support for the foreseeable future (Howard et al 2018).

Table 8.3: Functionality of The Ethiopian National Immunization Advisory Group,2017

	WHO Joint Reporting Forms (JRF) indicators	E-NITAG 2017 Remarks
1	Legislative or administrative basis for the advisory group;	The Minster endorsed the TOR and sent appointment letter to core members
2	Formal written terms of reference;	TOR approved
3	At least five different areas of expertise represented among core members (i.e. epidemiology, immunology, infectious diseases, paediatrics, public health);	Need to consider expanding expertise e.g. social science, economic/financial expert, pharmacologist etc. (See Table 6.1)
4	At least one meeting per year;	Conducted four in the first year (2016-2017)
5	Circulation of the agenda and background documents at least one week prior to meetings;	Yes
6	Mandatory disclosure of any conflict of interest …	Signed and deposited at the secretariat, meeting chair would ask if addition COI issues arise after handing in the signed COI form

9. INTRODUCTION PROCESSES

According to a study that investigated national process of new vaccine adoption (Burchett 2012), decisions to adopt new vaccines are said to be political by nature. The main drivers influencing decisions were the availability of funding, political prioritization of vaccination or the vaccine-preventable disease and the burden of disease. Other factors, such as financial sustainability and feasibility of introduction, were not considered as influential.

As more and more new vaccines are developed and brought to the market, governments have to make decisions about which vaccinations to include in public programs (Houweling et al. 2010). Bearing in mind the public nature, the factors that determine a vaccine suitability for inclusion in a communal vaccination program have been based on seriousness and extent of the disease burden; effectiveness and safety, acceptability, efficiency, and priority of the vaccination. These criteria provide a framework for the systematic examination of arguments for and against the inclusion and prioritization of particular vaccinations. The proposed assessment framework including the selection criteria can take full account of the values and specificities as they may differ between situations and countries; the transparency of the approach may help to clarify which elements of the assessment are pivotal in specific situations. Using the criteria furthers a trustworthy, transparent and accountable process of decision-making about inclusion of new vaccinations in public vaccination programs and may help to retain public confidence (Houweling et al. 2010).

A well-functioning vaccination program is a fundamental ingredient of successful public health interventions against infectious diseases (Hardt et al. 2016). National governments in developing countries can be successful in saving more lives if they develop the expertise to make the best technical decisions about immunization programs; take responsibility for helping to pay for and distribute vaccines; and are supported by strong partnerships with international organizations (Andrus et al. 2011). In particular, collaborative approaches to solving scientific, policy, and resource obstacles - as well as new partnerships among emerging economies and vaccine development organizations - will be critical to developing new vaccines that could achieve public health potentials to save lives and reduce the burden of diseases (Barker et al. 2011). Concerted efforts to communicate and advocate for vaccines prior to licensure are critical in the process of introducing new vaccines. The key strategies in

this regard focus on consolidating existing coalitions under one strategic umbrella, urgently convening stakeholders to formulate the roadmap for integrated prevention and control, and improving the dissemination of scientific knowledge in the specific area (Carvalho et al. 2016).

Studies have shown that a number of factors such as country per-capita gross domestic product, vaccine cost, immunization program strength, disease burden, disease treatment cost, access to external funding and the political and institutional capacity to decide and implement the introduction correlate with higher probability of introduction. Others have identified four necessary conditions that are jointly sufficient for the successful introduction of a new vaccine (Pentavalent in Indonesia), namely (a) an evidence-based vaccine use recommendation, (b) sufficient domestic financing capacity, (c) sufficient domestic vaccine manufacturing capacity or guaranteed source of procurement and (d) political support for introduction (Hadisoemarto et al 2016). Ideally, decision to introduce a vaccine against a particular disease should be based on a systematic review of data on the magnitude and cost of the disease and the vaccine's safety, efficacy, cost-effectiveness, and programmatic feasibility within the country context. The process will require strong leadership and coordination among the various activities to ensure adequate and timely funding, and availability of sufficient other resources (MCHIP 2014).

An independent advisory mechanism (see above) or an ICC as in Ethiopia previous to the establishment of NITAG, is required to oversee these activities (Burchett et al. 2012, Molla et al. 2015). This creates a strong team with multiple skill sets to ensure adequate coordination within the team and with partners, of various program areas needed for vaccine introduction. While the mechanism is expected to undertake multiple tasks, it could focus on 1) communication and advocacy, 2) research and surveillance, and 3) coordination of programmatic activities such as finance, supply and vaccine logistics (Hajjeh et al. 2010). The plan should target meeting the Decades strategic objectives (Box 9.1) and should always be coordinated with the global vaccine action plan (GVAP), the Regional Strategic Plan for Immunization 2014–2020, and with global and African political agreements and compacts

Box 9.1: Strategic Objectives for the Decade of Vaccines

All countries commit to immunization as a priority

1. *Individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility*
2. *The benefits of immunization are equitably extended to all people*
3. *Strong immunization systems are an integral part of a well-functioning health system*
4. *Immunization programs have sustainable access to predictable funding, quality supply and innovative technologies*
5. *Country, regional, and global research and development innovations maximize the benefits of immunization*

(Source WHO 2013, WHO AFRO 2017)

on health and immunization (Kochhar et al. 2013, WHO AFRO 2017).

It should also take account of important new directions such as 1) moving from supply-driven to demand-driven community immunization approaches, with Member States mobilizing local communities; 2) moving from globally-driven immunization agendas to nationally-owned immunization programs, with increased national budget allocations; 3) going from single-stream program structures to integrated health system approaches, with routine immunization as the bedrock of all immunization activities within a robust primary health care (PHC) system; 4) placing greater emphasis on the life-course approach to immunization (WHO AFRO 2017). The most important challenges in this connection is developing the capacity to make evidence-based new vaccine policy decisions and actually distributing the new vaccines to those who will most benefit from them. These require country-specific introduction plans as existing capacity differ by country (Lim et al. 2016).

9.1 Pre-Introduction Decisions

9.1.1. Selecting the Vaccine Product

In selecting vaccine products, polysaccharide vaccines are said to be poorly immunogenic in infants; however, when they are conjugated with a suitable protein carrier, the resulting polysaccharide–protein conjugate vaccines have been shown to be immunogenic in infants, to induce immunological memory, and to protect against nasopharyngeal colonization of *Hemophilus influenzae* type b as well as reduction in mortality from pneumonia (Adegbola 2012). Similarly, systematic reviews have also shown that the administration of conjugated vaccines has beneficial marginal effects in reduction of morbidities from vaccine preventable diseases (Arguedas et al 2011).

Second generation human papillomavirus (HPV) vaccines are said to be more affordable, cross-protective. They may be delivered in fewer doses and without needles, through inhalation, or oral or intra-vaginal administration, and will reduce the costs for expensive Pap screening programs and the burden of precursor lesions (Gersch et al 2012).

The selection of a vaccine involves assessment of availability of vaccine supply and the:

- Performance and characteristics of available vaccines

The vaccine itself needs to be safe and immunogenic inducing, ideally life long, broad protective coverage against the prevalent strains of the targeted pathogen and new strains that might emerge following the introduction of the vaccine. It should also be thermo stable and amenable to needle-free delivery and these attributes confirmed by in-country trials

(Maclennan 2013). However, in spite of WHO and partners attempt to enable countries to define and further develop their own regulatory policies, most LMIC essentially depended on WHO's vaccine prequalification process as the process could be onerous (Mantel and Wang 2012). Ahonkhai et al (2016) recommend leveraging or relying on the findings from reviews already performed by competent regulatory authorities for product approval, in addition to optimizing the process and requirements for product approval by regulatory bodies of home countries.

- Economic and financial issues

Affordability is key for the introduction of new vaccines into low-income countries (Maclennan 2013) but new vaccine pricing, a complicated process that could have substantial long-standing scientific, medical and public health ramifications (Lee and McGlone 2010), is an area on which most LMIC have little influence.

9.1.2. Deciding Who Is Eligible For the New Vaccine

Preparation for new vaccine introduction should include solid models forecasting how many individuals will likely benefit from the vaccine introduction, the coverage that should be achieved by the intervention and when (Kochhar and Seeber 2013). Based on these, supply forecasting exercises for the new vaccine estimate future consumption based on the number of age-eligible children born in the year after introduction (i.e. the new birth cohort) as the demand. In addition, potential wastage and a buffer stock are estimated to calculate the number of doses required in Year 1. If the immunization also includes a 'backlog cohort' (I.e. the older children who are eligible for vaccination at the time of introduction), the actual demand for vaccines may increase (Williams et al 2016). Epidemiologic studies are recommended to establish the burden and risk factors for a given disease, as well as to establish geographical and age related immunity gaps before the introduction of vaccines targeting that specific disease (Chotta et al 2017).

9.1.3. Revising the Immunization Schedule

All vaccines need to be examined for their non-specific effects and sex-differential effects as this has potential implications, for instance, on whether to choose standard or high titer measles vaccine. According to the analysis by Peter et al (2016), two doses of measles vaccine administered at 4.5 and nine months of age reduced mortality between 4.5 and 36 months by 30% (6–48%) compared with the standard administration of the vaccine at nine months of age. Assessing the indirect effects of some vaccines is also critical among high-risk groups such as HIV-infected persons that have an impaired immune response to polysaccharide vaccine, and who may require conjugate vaccines. Similarly, the introduction in 2010 of

a 10-valent pneumococcal conjugate vaccine (PCV10) in Brazil's national immunization program has led in the reduction of hospitalization of children due to pneumonia. On the other hand, new vaccines are needed that offer serotype-independent protection. Vaccines containing proteins that are common to all pneumococcal serotypes could provide broad protection to children (Alderson 2016).

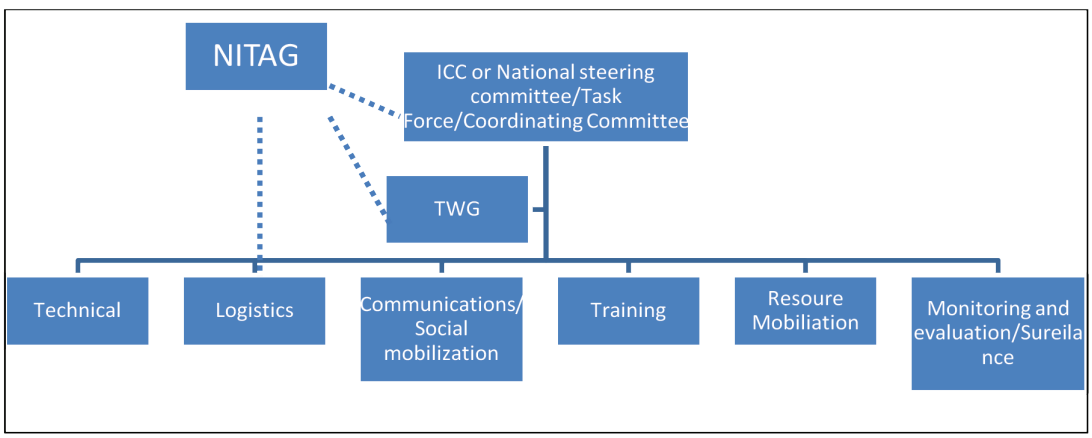
The decision to introduce a new vaccine should include on how it will fit into the existing immunization schedule and the impact of any changes on existing platform/ the national immunization program and on the health system in general should be thoroughly considered (Kochhar and Seeber 2013). New vaccines envisaged to be introduced in the near future include the expanding immunization beyond the first year of life – for example, second dose of measles containing vaccine at the second year – was also mentioned. Other new vaccines considered are said to include those for: yellow fever, malaria, and rubella. The introduction of MCV2 and HPV is also said to have already brought a new target group to the immunization system.

9.2 Preparing for the Vaccine Introduction

9.2.1. Establishing Organizational Structures to Prepare for New Vaccine Introduction

As indicated above (Section 7), all relevant MOH departments and other relevant stakeholders should be represented on the technical committees (Fig. 9.1 for examples) preparing the vaccine introduction (MCHIP 2014).

Fig 9.1: Examples of Stakeholders for Vaccine Introduction
(Source: Adapted from MCHIP 2014)



See 6.2 for current status of E-NITAG

9.2.2. Budgeting and Securing Funding For New Vaccine Introduction and the Long Term

The decision making process regarding new vaccine introduction should follow a systematic approach that considers: existing evidence on efficacy, potential impact, and cost-effectiveness the vaccine to be introduced (Burchett et al. 2012). Economic studies should be considered before the introduction of vaccines to give policy makers indications of how much people were willing to contribute financially towards vaccination programs (Birhane et al. 2012). In particular, cost-effectiveness analysis, despite some limitations, has been seen to be helpful for developing countries to perform informed decisions about the introduction of new vaccines (Castaneda-Orjuela 2011, Luyten et al. 2015). Its proper conduct could lead to better policies and thus more worthwhile and good-value programs to benefit children's health in developing countries (Gauvreau et al. 2012). In conducting cost-effectiveness analyses of vaccine introduction, it is recommended that one should also consider costs of expanded program of immunization, in addition to those of vaccine procurement, since several factors like personnel, cold chain, or social mobilization can be substantially affected by the introduction of new vaccines (De la Hoz-Restrepoa et al. 2013).

Lessons learned for successful vaccine introduction include the importance of coordination between political and technical decision makers, adjustments to the cold chain prior to vaccine introduction, and the need for detailed plans addressing the financial and technical sustainability of introduction (de Oliveira et al. 2016).

Budgeting and securing funding for new vaccine introduction is becoming increasingly important as the cost of immunizing children continues to rise. Government expenditures on routine immunization in GAVI-eligible countries are positively and significantly correlated with gross national income (GNI). Projecting forward and assuming continued annual GNI growth rates of 10.65%, countries could be spending $60 per infant by 2020 if national investment functions increase 4-fold. Given the political will, this result implies countries could fully finance their routine immunization programs without cutting funding for other programs (Nadar et al. 2015). Vaccine prices are the main cost driver in immunization programs and cost to fully immunize a child is rising with new vaccine prices as the major contributors. Thus, price for all recommended vaccines increased by 68 times between 2001–2014 (Table 9.1).

Table 9.1: Vaccine Price, 2001 and 2014 (De la Hoz-Restrepoa 2013)

Year	Vaccine Prices	Vaccines
2001	$0.67	6 initial antigens (OPV, DTP, measles, BCG)
2014	- $32.09 fully immunized boy (11 antigens)	- 11 antigens in total
	- $45.59 fully immunized girl (11 antigens + HPV)	- 6 initial antigens + Hepatitis B, PCV, rubella, rotavirus, IPV, and *Haemophilus influenza* type b (Hib)

The total cost of vaccination and cost per fully-vaccinated individual can be reduced substantially by introducing a low-priced vaccine, which could possibly be produced in LMCs (Sarker et al. 2015). Vaccine manufacture may prima facie seem an economic growth opportunity, however, the complexity and high fixed costs of vaccine manufacturing limit potential profit. Further, for most lower and middle income countries a large majority of the equipment, personnel and consumables will need to be imported for years, further limiting benefits to the local economy (Plotkin 2017).

The dramatic growth in demand for traditional and new vaccines resulted in increased emphasis on ensuring a "healthy" vaccine market, defined as a market with adequate supply, reliable quality, and appropriate prices to meet global and national demands for new and existing vaccines (Nicholas 2017).

As the vaccine market has evolved, so has the emphasis on high-quality production and increased adoption of multivalent vaccines, and safety of vaccines. Stringent current Good Manufacturing Practice (cGMP) standards, WHO prequalification requirements, and tighter oversight of and by national regulatory authorities (NRAs) require companies and countries to continually invest in equipment and facilities modernization and staff training to comply with quality and safety standards. Moreover, a much larger market size is needed to achieve economies of scale today. As countries include combination and other complex vaccines in EPI schedules, manufacturers Technology transfer is a lengthy and expensive process that requires deep commitment as well as aligned value for each partner. Government commitment, policies supporting access to capital, and continuous sponsorship of an independent NRA are critical for the long-term viability of manufacturers (Nicholas 2017).

Key target objectives for improving access to new vaccines also include overcoming intellectual property obstacles, streamlining regulatory pathways for bio-similar vaccines, and reducing market entry timelines for developing-country vaccine manufacturers by transfer of technology and know-how. This could, for example, be done through an intellectual property, technology, and know-how bank as a new approach to facilitate widespread access

to new vaccines in low- and middle-income countries by efficient transfer of patented vaccine technologies to multiple developing-country vaccine manufacturers (Carger 2014). Donors that contribute to GAVI expect that it will use their resources to help countries introduce more new vaccines and extend equitable and sustainable immunization coverage to the remaining "fifth child"—or the children in remote areas far from health clinics who are the most challenging to reach (Shen et al 2016).

In Ethiopia, the main partners financing the immunization program are GAVI (61%), national and sub national government (33%), UNICEF (2%), WHO (2%), and other partners (1%). Main weaknesses in the national immunization financing system include low visibility of immunization financing at subnational level; gaps in mobilizing local resource for immunization; poor resource mapping capacity especially at sub-national level; weak financial utilization and timely disbursement at all levels; low multi-sectorial response particularly in development and investment corridors; and delay in financial disbursement from partners (Newall & Hutubessy 2014).

The ultimate success of international development assistance for health should be measured in its gradual disappearance, after having left a lasting positive impact on populations and strengthened the foundations of further economic development. To avoid disrupting lifesaving immunization programs and to ensure the long-term sustainable impact of GAVI's investments, it is vital that governments succeed in transitioning from development assistance to domestic financing of immunization programs (Kallenberg et al. 2016).

9.2.3. Determining Country Readiness and Appropriate Timing for Vaccine Introduction

Early planning is of critical importance for country decisions on new health interventions. While there is always a risk that an intervention under development fails, a small amount of time invested in planning for its possible use has the promise to pay off immensely down the road. Proper planning holds promise for better public health practice and greater public health impact through accelerated and informed decisions on the use of a new intervention once available (Brooks & Ba-Nguz 2012). As the mechanisms for discovery, development, and delivery of new vaccines become increasingly complex, strategic planning and priority setting have become ever more crucial. Traditional single value metrics such as disease burden or cost-effectiveness no longer suffice to rank vaccine candidates for development (Madhavan et al. 2015). In addition, it is important to create a sense of trust among governments and other stakeholders to reduce suspicions about new vaccines that may arise in the context of vaccine introduction in developing country settings (Cover et al. 2012).

In Ethiopia, key informant responses suggest that there are strengths the country can leverage in the introduction of new vaccines. These include government commitment, regional ownership, availability of well-organized annual plan, strong local and international partnership, as well as continuous increasing trend of coverage through the past several years with provision across all levels of health institutions. On the other hand, the need for building human resources capacity and strong competency and retention mechanisms for providing quality services was among the opportunities for improvement. Current clashes and displacements in some localities that may increase the risk of disease transmission and dropouts, poor and inflated reporting in some instances, lack of staff incentives and motivation, absence of regular defaulter tracing system, deficient cold-chain management and maintenance, high turn-over of staff, recurrent measles epidemic in the South are considered as some of the weaknesses and threats to the program. Moreover, almost all respondents voiced their concern on the high degree of dependency on external funding that threatens the sustainability of the program.

Introduction of any new health interventions, including introduction of new vaccines, in a country requires scientific, logistic and economic considerations. Most often, lack of scientific epidemiological data on disease burden, poor health system, lack of procurement of sufficient quantity of vaccines, lack of trained human resource, poor vaccine coverage are cited as important stumbling blocks in the introduction of new vaccines in the developing countries national program (Duta 2016). Prioritization and best use of the vaccine (e.g. how, when and where to use) could be challenges. Once introduced, programs could face regulatory, cold chain logistics and vaccine coverage and uptake hurdles (Hsiao et al. 2017).

The introduction and use of new vaccines has often been characterized by rapid uptake in the countries where the disease burden is least and delayed uptake in the countries where the disease burden is greatest. Differences in the economic power of countries are an obvious contributor to the delays in uptake of newly introduced vaccines. However experience with 'economics-only solutions' like the provision of free vaccines have not overcome the problem and as a result have illustrated that the obstacles are more diverse than economics alone (Levine 2010). Hurdles to attaining adequate coverage rates include introduction without adequate preparation; insufficient supply chain capacity and management; poor communication between organizations and with the public; and data collection systems that were insufficient to meet information needs (Olyinka et al. 2017).

Widespread use of SMART Vaccines will require compilation of a comprehensive data repository for numerous relevant populations-including their demographics, disease burdens and associated treatment costs, as well as characterizing performance features of potential

or existing vaccines that might be created, improved, or deployed. Finding strategies to bridge the gap to a comprehensive data repository remains the most important task in bringing SMART Vaccines to full fruition, and to support strategic vaccine prioritization efforts in general (Madhavan et al. 2015).

Key informant results indicate that major stakeholders in the process of introduction of new vaccines in Ethiopia include the MOH, UN agencies, WHO and UNICEF and other development partners such as the Inter Agency Coordination Committee. The FMHACA also plays a critical role in ensuring the safety and effectiveness of introduced vaccines and checking whether the products/vaccines are WHO pre-qualified. Introduction of new vaccines should involve a consultative process and technical inputs from the NITAG. As demonstrated in the process of some of the new vaccines introduced recently (such as PCV), pilot studies before approval could be useful.

Key informants recommendations for introduction of emphasized the need for serious consideration of the financial side of the process, and not limited to base decision on epidemiologic and disease burden analysis. The results also suggest that the NITAG should be independent and make evidence-based decisions both from technical and socioeconomic perspectives. Planning should be done well ahead of time through the involvement the academia and researchers and include sustainable financing and support mechanisms in the long haul. Overall establishing/ strengthening vaccine intelligence system in Ethiopia is considered as a novel and highly desirable idea by all the respondents as it is said to facilitate efficient management of the cold chain and vaccine logistics management system. It should also involve stakeholders such as the media (social media, health media etc.).

9.2.4. Assessing, Upgrading and Expanding Cold Chain, Logistics, and Waste Management Systems to Accommodate New Vaccines

Implementing Electronic Vaccine Intelligence Network (eVIN) is a technology system to digitize the stock of vaccines and to monitor the temperature of the cold chain with the help of a smartphone application. One of the most important components of the immunization program is the vaccine supply and cold chain to keep vaccines safe and efficacious and eVIN help in better management of vaccine supply chain. eVIN platform provides an integrated solution to address widespread inequities in vaccine coverage by overcoming infrastructure bottleneck, poor information management which often leads to overstock or stock out of vaccines in storage centers. This will ensure efficient vaccine logistics management with help of systemized record management system. eVIN streamline the vaccine flow network and therefore contributes towards strengthening health systems and ensures that idea of universal immunization is properly implemented (Gill 2017, Kapuria et al. 2014). In Ethiopia,

even though logistics and cold chain are key components of the immunization program, key informants have concerns on the adequacy and the quality at the storage sites and point of delivery as well as on the practice of monitoring the system in place. Regarding logistics and supply management, the fact that vaccine distribution and management is transferred to Ethiopian pharmaceutical agency is among the changes made in the supply system.

9.2.5. Revising Vaccine Management Systems to Accommodate New Vaccines

Regulatory challenges for developing countries may be overcome with better communication; global collaborations and partnerships for leveraging investments and enabling uninterrupted supply of affordable and suitable vaccines. Moving further into the Decade of Vaccines requires renewed commitment to shared responsibility toward a world free of vaccine-preventable diseases (Pagliusi et al. 2015). There are needs for research and development of new and better vaccines and strategies to improve performance of available vaccines for their implementation in countries where they are less effective, but will still save a significant number of children's lives annually (Babji & Kang 2012).

9.2.6. Building Health Worker Capacity for Safe and Effective Use of Vaccines

Rational and wider use of vaccine entails improving burden of diseases data, use of transmission dynamic models, conducting economic evaluations, as well as learning from experiences of pilot projects on human resource needs (Crump 2015). Among the programmatic issues raised by the report on post-introduction evaluations for pneumococcal conjugate vaccines in African countries, for example, include: the need for accurate data to define target populations, accompanied by clear messages to health workers and the community to prioritize target populations. In addition, health worker knowledge about the protection provided by PCV are said to be crucial. Furthermore, capacity building issues – in terms of training, supportive supervision, as well as monitoring of adverse events were other important issues raised by the report [(US Centers for Disease Control and Prevention (CDC) 2016)].

"Capable health workers are critical to the effective and safe use of any vaccine, whether new or old. With the addition of new vaccines comes greater complexity in vaccine handling, administration, interpersonal communication, and recording and reporting data on their use" (MCHIP 2014). In addition, "The science of vaccines has become more complex, making effective, clear and consistent communication for healthcare workers and caregivers critical to the uptake of and adherence to lifesaving vaccination." (Baleta et al. 2012). Therefore, all those involved in the new vaccine introduction should be given adequate orientation and training tailored for the introduction.

9.2.7. Communicating and Creating Demand for New Vaccines and Immunization

The very successes of immunization programs with the development of many new vaccines and innovative finance mechanisms means that the public is better informed about developments in immunization. Concurrently, communication technology is developing at a rapid rate exposing the public to confusing and conflicting information about the need for vaccination. Providing parents and other community members with information on immunization, health education at facilities in combination with redesigned immunization reminder cards, regular immunization outreach with and without household incentives, home visits, and integration of immunization with other services may improve childhood immunization coverage in LMIC [Oyo-Ita et al. 2016, WHO 2018c].

Even though vaccine hesitancy is rather limited in Ethiopia (Larson et al. 2016), continued vigilance and quick response (Corcoran et al 2018) is required *as* a study in Addis Ababa indicates that high vaccine hesitancy was strongly associated with infants' untimed vaccination and "that increased efforts to educate community members and providers about vaccines may have a beneficial impact on vaccine timeliness in Addis Ababa" (Masters et al. 2018). According to the experience in South Africa, putting in place proper efforts for advocacy with decision makers, social mobilization and communication with parents and caregivers have been key components of a successful introduction of new vaccines into childhood immunization schedules (Baleta et al. 2012).

9.2.8. Revising Health and Immunization Management and Reporting Forms and Materials to Include the New Vaccine

Good country-level governance is an imperative pre-requisite for the successful early introduction of new vaccines into poor African nations. Enhanced support measures may be required to effectively introduce new vaccines to countries with low governance scores. For a new vaccine programs to succeed, special considerations and criteria should be applied to different countries. Countries with higher governance scores can be expected to respond faster to GAVI and other international vaccine initiatives (Glatman-Freedman et al. 2010, Andrus et al. 2011).

9.3 Monitoring and Evaluating the Vaccine Introduction

9.3.1. Coverage Monitoring For the New Vaccine

According to the *Global Vaccine Action Plan 2011–2020* (GVAP) (WHO 2013), all countries are expected to reach ≥90% national coverage, 80% in all districts, for all vaccines in the country's routine immunization schedule by 2020 (Casey et al 2017, Feldstein et al. 2017). "Immunization programs [In countries where vaccines have been recently introduced]

must closely review vaccine implementation and coverage to identify actions necessary to ensure equity and optimize impact" (Loharikar et al. 2016). Vaccination coverage is an important public health indicator for measuring the success of the vaccine introduction and identifying low-performance areas and bottlenecks but faces several challenges in LMIC. Administrative reports are notoriously deficient (Feldstein et al. 2017). Vaccination coverage surveys are susceptible to numerous challenges including selection bias and information bias (Cutts et al. 2013, Danovaro-Holliday et al. 2018). Thus, "… obtaining high-quality, credible coverage data for the first year after a new vaccine has been introduced can be extremely challenging" (MCHIP 2014). Therefore, improvement is required including high resolution age-structured mapping of childhood vaccination coverage (Utazi et al. 2018).

"In general, covering as many diseases as possible, ensuring vaccine potency and achieving high immunization coverage are essential requirements for childhood immunization to have the desired public health impact of decreasing mortality and morbidity, and possibly eliminating some of the vaccine-preventable diseases … Increasing immunization coverage involves two key elements: increasing access to immunization services and reducing dropout rates" (Zewdie et al. 2016).

9.3.2. Post-Introduction Program Monitoring and Supervision

The number of vaccine doses administered worldwide continues to increase as new vaccines are developed and made available, and more people have access to immunization services. Development of immunization programs in LMICs has increased immunization coverage, which in turn has led to a reduction in vaccine-preventable diseases. However, as vaccine use has increased in LMICs, so has public attention to vaccine safety issues, as happened previously in high-income countries. This has created additional vulnerability for all immunization programs. Vaccine safety is high and serious adverse effects relatively rare as shown, for example, by well documented follow ups in USA [(Health Resources and Supplies Agency (HRSA) 2017)]. Whether or not they are well founded, concerns about serious adverse events following immunization may rapidly undermine public confidence and become a serious threat to effective vaccination strategies, eroding the enormous gains in disease control achieved with decades of effort. It is thus imperative that post licensure vaccine safety surveillance is considered as an important component of a vaccine program (Andrews 2015).

Robust supportive supervision at all levels and possibly covering other health interventions besides immunization, is critical for monitoring performance of the immunization program on a regular basis and identifying key issues to address (MCHIP 2014). Particular attention

should be paid to those population groups that might be systematically missed using, for example, 'the equity dashboard' to facilitate equity monitoring (Arsenault et al. 2017). Better attention should also be paid to the proactive monitoring of the safety of vaccines in developing countries as, with increasing administered doses and with increased coverage, increase in Adverse Effect Following Immunization (AEFI) should be anticipated (Lie et al. 2018). "All countries, irrespective of the economic status of its population and technological advances, have room for improving vaccine safety monitoring" (Kochhar & Seeber, 2013, see also WHO 2014, Larson et al. 2016, Olsson et al. 2016, Lei et al. 2018).

Measures should be taken to address **strategic goals to optimize vaccine safety.** The WHO has developed the Global Vaccine Safety Blueprint in 2011 that sets three main strategic goals to optimize the safety of vaccines through effective use of pharmacovigilance principles and methods: to ensure minimal vaccine safety capacity in all countries; to provide enhanced capacity for specific circumstances; and to establish a global support network to assist national authorities with capacity building and crisis management (Amarasinghe et al. 2013). Among the safety issue that may potentially affect vaccine uptake include concerns related to intussusception with consequent age restrictions on rotavirus vaccination, contamination with porcine circovirus, vaccine-derived reassortant strains and hospitalization in newborn nurseries at time of administration of live oral rotavirus vaccine (Aliabadi et al. 2016). In addition, some strains of BCG vaccine might contribute to increased incidence of lymphadenitis in children (Alrabiaah et al. 2012).

Experience in countries with long-standing immunization programs show that, as vaccine-preventable diseases are brought under control and memories fade, public attention will shift to vaccine safety and sustained efforts should be made to provide evidence base and adequately inform the public for the remaining tasks. This is even more important for vaccines such as PCV where serotypes not covered could increase (Mackenzie et al. 2012). The more so in LMIC where fragmented healthcare systems and weak regulatory oversight, the pharmaceutical supply chain constrain pharmacovigilance and substandard/spurious/falsely labeled/falsified/counterfeit (SSFFC) medicines and vaccines can easily penetrate the supply chain (Olsson et al. 2016).

9.3.3. Implementation research

Implementation research has been identified as an important step toward achieving high vaccine coverage and the uptake of desirable new vaccines by the Decade of Vaccines Collaboration (DoVC) Research and Development (R&D) Working Group. However, implementation research is highly contextual depending on social, cultural, geographic, and

economic factors to make the findings useful for local, national, and regional applications; and complex requiring participation of stakeholders from diverse backgrounds to ensure effective planning, execution, interpretation, and adoption of research outcomes. Meeting UNICEF's Global Immunization Vision and Strategy (GIVS) goal for all countries to achieve 90 percent national coverage and 80 percent coverage in every district for DPT3 will require research strategies including: (1) social and behavioral science research to increase confidence in a vaccine; (2) an emphasis on context-specific research; and (3) establishing a network of Centers of Excellence for implementation research, including provision for core funding for such centers" (Arora et al. 2013).

10. CONCLUSIONS

- Immunization has solid track records in improving health and economic outcomes worldwide. In spite of these demonstrable successes, infectious diseases continue to pose major threats to health in low-income countries such as Ethiopia. Ethiopia has, in recent years, relatively successfully introduced new vaccines and the immunization program in general has strongly impacted health and economic developments even though there are still some problems with equity, coverage and quality of service. Thus, as this review demonstrates, in spite of laudable efforts in recent years, Ethiopia continues to suffer from some of the lowest vaccination rates on the continent and an unnecessarily high burden of potentially preventable diseases. Therefore, there will be continued **pressure to adopt new and improved vaccines, technologies, and procedures** as soon as possible and issues of prioritization and sustainability are bound to emerge.

- Vaccines remain highly acceptable interventions in Ethiopia but, with continued successes, more **'health system' and socio-economic/financial opportunities and even more challenges should be anticipated**. Care should also be taken not to overburden a relatively well functioning health system by too ambitious introduction of new vaccines and/or new procedures. The key to success of introducing a new vaccine in a developing country such as Ethiopia is how best it can be integrated with other intervention programs of the country.

- The health/vaccine delivery system in Ethiopia exhibits several weaknesses. There is need for strong advocacy and legislation that mandates the introduction of new vaccines, approve budgets required by the immunization program, establish mechanisms to finance and monitor immunization services. Several challenges in the introduction of new vaccines are related to the **decision-making process** that is relatively little understood in low-income countries, which lack experience in proactive planning, and have limited understanding of the impacts of introducing new vaccines and approaches.

- Vaccine introduction process requires sound evidence base on the epidemiology and burden of disease (including the distribution of serotypes or strains if relevant to vaccine policies) and the safety, efficacy and relative cost-effectiveness of the vaccine as a solution. Wide-reaching analyses of technical, political and programmatic considerations of decision-making are required in the introduction of new and underutilized vaccines in resource low income a country. As demonstrated in this review, national governments in developing countries can be successful in saving more lives if they develop the expertise to make the best technical decisions about immunization programs.

- With increasing number of new and improved vaccines becoming available, decisions on which to adopt into routine programs become more frequent and complex; countries and NITAGs have to adapt to this complexity. The need to make important decisions about the use of new vaccines provides an excellent opportunity for countries to consider the use of broader advisory committees to deliberate and address strategic issues and health priorities at national level. The current program is highly dependent on external funding. In spite of promising global commitments such as Global Vaccine Action Plan (GVAP), Vaccine Procurement Baseline (VPB) proposal, calls to make Vaccine Procurement Assistance (VPA), and a clearly defined and specific sub-category of ODA, measures should be taken to meet anticipated financial flow gaps for vaccination in the future. Countries also need to prepare for ramp down after PEI and the country's promotion to LMIC.

- The launching of E-NITAG is promising and critical to ensuring informed and evidence-based recommendations in introduction and financial sustainability of vaccines as the country will face several opportunities & challenges. However, it requires **strengthening** (Box 9.2) with adequate internal and external coordination and networking as well as support, as introduction of new vaccines has major implications, including:

Box 9.2: Strengthening E-NITAG

- Bring together all stakeholders with E-NITAG as a hub of independent technical advisor to reflect and decided on, as appropriate. See details in sections:
  - Pre-introduction issues
  - Preparing for the Vaccine Introduction
  - Monitoring & Evaluating Vaccine Introduction
- Consolidate independence
  - Define clearly term of service and mechanism of induction of new members
  - Improve legal framework [from current letter of Minister to more formal status] …
- Strengthen the Secretariat/unit, develop capacity to follow up and regularly update on:
  - decisions by E-NITAG
  - liaisons with RNITAG and other NITAGs
  - M&E tasks specifically mandated by E-NITAG
  - research/studies (disease burden, cost effectiveness/benefits etc.) requested by E-NITAG …

- comprehensive assessment based on WHO/ international recommendations/ commitments
- generating and assessing local epidemiological data
- assessing the affordability, cost-effectiveness and sustainability, and
- identifying & ensuring additional expertise to facilitate well- informed decision making

REFERENCES

1. Adegbola. Childhood pneumonia as a global health priority and the strategic interest of the Bill & Melinda Gates Foundation. Clinical Infectious Diseases 2012;54(S2):S89–92.

2. Adjagba, et al. The NITAG Resource Centre (NRC): One-stop shop towards a collaborative platform. Vaccine. 2015 (33), pp. 4365–4367.

3. Aguado, et al. From epidemic meningitis vaccines for Africa to the meningitis vaccine project. Clinical Infectious Diseases. 2015;61(S5):S391–5.

4. Ahonkhai, et al. Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. PLoS ONE 2016; 11(11): e0166515.

5. Alderson. Status of vaccine research and development of pediatric vaccines for Streptococcus pneumonia. Vaccine. 2016;03.107.

6. Alebachew and Ortendahl. GAVI Health System Strengthening Support Evaluation: Ethiopia Case Study. RFP-0006-08. Final Version - August 2009.

7. Alcock. Long-Term Thermo-stabilization of Live Poxviral and Adenoviral Vaccine Vectors at Supra-physiological Temperatures in Carbohydrate Glass. Sci Transl Med. 2010;2(19ra12).

8. Aliabadi, et al. Potential safety issues and other factors that may affect the introduction and uptake of rotavirus vaccines. Clin Microbiol Infect. 2016; 22 (Suppl 5): S128–S135.

9. Alrabiaah, et al. Outbreak of Bacille Calmette-Guérin-related lymphadenitis in Saudi children at a university hospital after a change in the strain of vaccine. Ann Saudi Med. 2012: 32(1): 4-8.

10. Amarasinghe, et al. Effective vaccine safety systems in all countries: A challenge for more equitable access to immunization. Vaccine. 2013; 31S:B108– B114.

11. Aminu, et al. Diversity of Rotavirus VP7 and VP4 Genotypes in Northwestern Nigeria. The Journal of Infectious Diseases. 2010; 202(S1):S198–S204.

12. Andrews. Methodologies for vaccine safety surveillance. London; Public Health England. 2015.

13. Andrus, et al. Challenges to building capacity for evidence-based new vaccine policy in developing countries. Health Affairs. 2011;30(6):1104–1112.

14. Arguedas, et al. Prevenar experience. Vaccine 2011; 29S:C26– C34.

15. Arsenault, et al. An equity dashboard to monitor vaccination coverage. Bull World

Health Organ 2017;95:128–134.

16. Arora, et al. The need for targeted implementation research to improve coverage of basic vaccines and introduction of new vaccines. Vaccine. 2013, 31S;B129– B136.

17. Babji and Kang. Rotavirus vaccination in developing countries. Current Opinion in Virology. 2012, 2:443–448.

18. Baleta, et al. Meeting the need for advocacy, social mobilisation and communication in the introduction of three new vaccines in South Africa – Successes and challenges. Vaccine. 2012, 30S C66– C71.

19. Ba-Nguz A. National Immunization Technical Advisory Groups (NITAGs). 10th Annual African Vaccinology course, Cape Town, November 2014.

20. Barker, et al. The challenges of developing new tuberculosis vaccines. Health Affairs. 2011, 30(6):1073–1079.

21. Bårnes, et al. Prevalence and epidemiology of meningococcal carriage .in Southern Ethiopia prior to implementation of MenAfriVac, a conjugate vaccine. BMC Infectious Diseases. 2016; 16:639.

22. Bar-Zeev, et al. Cost-effectiveness of monovalent rotavirus vaccination of infants in Malawi: A post-introduction analysis using individual patient–level costing data. Clinical Infectious Diseases. 2016;62(S2):S220–8.

23. Belete, et al. Routine immunization in Ethiopia. Ethiop J Heal Dev. 2015; 29(S1):2–7.

24. Bell S et al. Value and effectiveness of National Immunization Technical Advisory Groups in low- and middle-income countries: a qualitative study of global and national perspectives. Health Policy and Planning, 2019, 1–11. doi: 10.1093/heapol/czz027.

25. Bennie. Italy Passes Law Obliging Parents to Vaccinate Children - *Medscape* - May 19, 2017.

26. Berkley S. Vaccination lags behind in middle-income countries. Nature 2019,569: 309.

27. Bethony, et al. Vaccines to combat the neglected tropical diseases. Immunol Rev. 2011;239(1): 237–270.

28. Birhane, et al. Willingness to pay for dog rabies vaccine and registration in Ilocos Norte, Philippines. PLoS Negl Trop Dis. 2012;10(3):e0004486.

29. Blankenhorn, et al. Exceptional financial support for introduction of inactivated polio vaccine in middle-income countries. The Journal of Infectious Diseases. 2017;216(S1):S52–6.

30. Bezunesh, et al. Knowledge of mothers on poliomyelitis and other vaccine prevent-

able diseases and vaccine status of children in pastoralist and semi-pastoralist areas in Ethiopia. Ethiop. Med. J. 2013; 51 (Supplement 1): 59-66.

31. Bosch, et al. Comprehensive control of human papilloma virus infections and related diseases. Vaccine. 2013;31S: I1–I31.

32. Bregu, et al. Accelerating vaccine development and deployment: report of a Royal Society satellite meeting. Phil Trans R Soc B. 2011;366:2841–2849.

33. Brooks and Ba-Nguz. Country planning for health interventions under development: lessons from the malaria vaccine decision-making framework and implications for other new interventions. Health Policy and Planning. 2012;27:ii50–ii61.

34. Bryson, et al. A global look at national Immunization Technical Advisory Groups. Vaccine. 2010, 28S, A13–A17.

35. Burchett, et al. The impact of introducing new vaccines on the health system: Case studies from six low- and middle-income countries. Vaccine. 2014;32:6505–6512.

36. Burchette, et al. New Vaccine Adoption: Qualitative Study of National Decision-Making Processes in Seven Low- and Middle-Income Countries. Health Policy and Planning. 2012; 27(sup 2): ii5-ii16.

37. Caplan and Hotez. Science in the fight to uphold the rights of children. PLoS Biol. 2018, 18;16(9):e3000010.

38. Carvalho, et al. International Dengue Vaccine Communication and Advocacy: Challenges and Way Forward. Expert Review of Vaccines. 2016; (15) 4, pp.539-545.

39. Casey, et al. State of equity: childhood immunization in the World Health Organization African Region. The Pan African Medical Journal. 2017;27 (Supp 3):5.

40. Castaneda-Orjuela, et al. Cost-effectiveness of the introduction of the pneumococcal polysaccharide vaccine in elderly Colombian population. Vaccine. 2011; 29:7644–7650.

41. Chauke-Moagia and Mumbab. New vaccine introduction in the East and Southern African sub-region of the WHO African region in the context of GIVS and MDGs. Vaccine. 2012; 30S:C3– C8.

42. Chen and Zehrung. Desirable attributes of vaccines for deployment in low-resource settings. Journal of Pharmaceutical Sciences. 2013;102: 29–33.

43. Chotta, et al. Stray-Pedersen A. Rubella sero-prevalence among children in Kilimanjaro region: a community based study prior to the introduction of rubella vaccine in Tanzania. Journal of Pediatrics. 2017;43:63.

44. Clendinen, et al. Manufacturing costs of HPV vaccines for developing countries. Vaccine. 2016, 34, pp. 5984–5989.

45. Corcoran B, et al. Rapid response to HPV vaccination crisis in Ireland. The Lancet 2018; 391: 2103.

46. Cover JK, et al. Acceptance patterns and decision-making for human papillomavirus vaccination among parents in Vietnam: an in-depth qualitative study post-vaccination. BMC Public Health 2012, 12:629.

47. Crager. Improving Global Access to New Vaccines: Intellectual Property, Technology Transfer, and Regulatory Pathways. Am J Public Health. 2014, 104 (11), e85-91.

48. Crump. Building the case for wider use of typhoid vaccines. Vaccine. 2015; 04.033.

49. Cutts, et al. Measuring Coverage in MNCH: Design, Implementation, and Interpretation Challenges Associated with Tracking Vaccination Coverage Using Household Surveys. PLoS Med. 2013; 10(5): e1001404.

50. Danovaro-Holliday, et al. Collecting and using reliable vaccination coverage survey estimates: Summary and recommendations from the "Meeting to share lessons learnt from the roll-out of the updated WHO Vaccination Coverage Cluster Survey Reference Manual and to set an operational research agenda around vaccination coverage surveys", Geneva, 18–21 April 2017. Vaccine. 2018, 36; 5150–5159.

51. De la Hoz-Restrepoa, et al. Systematic review of incremental non-vaccine cost estimates used in cost-effectiveness analysis on the introduction of rotavirus and pneumococcal vaccines. Vaccine. 2013;31S:C80– C87.

52. De Oliveira, et al. Systematic documentation of new vaccine introduction in selected countries of the Latin America Region. Vaccine. 2013; Supp. 3, c114-22.

53. De Oliveira, et al. Pneumococcal conjugate vaccine introduction in Latin America and the Caribbean: progress and lessons learned. Expert Review of Vaccines. 2016;15(10), 1295-304.

54. Djingarey, et al. Effectively introducing a new meningococcal A conjugate vaccine in Africa: The Burkina Faso experience. Vaccine. 2012;30S:B40– B45.

55. Dockrell. Towards new TB vaccines: What are the challenges? Pathogens and Disease. 2016; 74, ftw016.

56. Dutta, et al. Learnings from Pentavalent Vaccine Introduction in India. Indian J Pediatr. 2016, 83(4):294-9.

57. Editorial. Vaccination in a "me first" era. The Lancet Global Health. 2018; 6: e811.

58. E-NITAG. Ethiopian NITAG Status. 13 November 2017; Addis Ababa, Ethiopia.

59. Feldstein, et al. Global Routine Vaccination Coverage, 2016. Morbidity and Mortality Weekly Report. 2017; 66(46): 1252-1255.

60. Feemster. Overview: Special focus vaccine acceptance. Human Vaccines & Immu-

no-therapeutics. 2013;9(8):1752-1754.

61. Fesenfeld, et al. Cost-effectiveness of HPV in low and middle income countries. Vaccine. 2013; 31,(37), 3786-3804.

62. Gauvreau, et al. The use of cost-effectiveness analysis for pediatric immunization in developing Countries. The Milbank Quarterly. 2012; 90(4):762–790.

63. Gersch, et al. New approaches to prophylactic human papillomavirus vaccines for cervical cancer prevention. Antivir Ther. 2012; 17(3).

64. Getahun, et al. Epidemiology of rubella virus cases in the pre-vaccination era of Ethiopia, 2009–2015. BMC Public Health. 2016;16:1168.

65. GHSA. A Global Health Security Agenda Roadmap for Ethiopia. March 9, 2016.

66. Ghazanfar, et al. Rotavirus vaccine — a new hope. J Pak Med Assoc. 2014; 64(10):1211-1216.

67. Gill. Unleashing the potential of technology in intelligent vaccine Management. ET-HealthWorld August 14, 2017.

68. Glatman-Freedman, et al. Factors Affecting the Introduction of New Vaccines to Poor Nations: A Comparative Study of the Haemophilus andomize Type B and Hepatitis B Vaccines. PLOS ONE. 2010; 5(11): e13802.

69. Gordon, et al. Introducing Multiple Vaccines in Low-and Middle-Income Countries: Issues, Opportunities and Challenges. Health Policy and Planning. 2012; 27: ii17-ii26.

70. Hadisoemarto et al. Introduction of pentavalent vaccine in Indonesia: a policy analysis. Health Policy and Planning. 2016, pp. 1–10.

71. Hajjeh, et al. Supporting new vaccine introduction decisions: Lessons learned from the Hib Initiative experience. Vaccine. 2010; 28, 7123–7129.

72. Hardt, et al. Vaccine strategies: Optimising outcomes. Vaccine. 2016;34:5591-6699.

73. Hawkes, et al. Vaccines to promote and protect sexual health: Policy challenges and opportunities. Vaccine. 2014; 32, 1610–1615.

74. HERSA. National Vaccine Injury Compensation Program Monthly Statistics Report. United States Department of Health and Human Services, Health Resources and Services Administration (HERSA), Updated 11/01/2017.

75. Horton, et al. Ranking 93 health interventions for low- and middle-income countries by cost-effectiveness. PLoS ONE. 2017; 12(8): e0182951.

76. Howard N et al. What works for human papillomavirus vaccine introduction in low

and middle-income countries? Papillomavirus Research 2017, 4:22-25.

77. Howard N et al. The role of National Immunization Technical Advisory Groups (NITAGs) in strengthening national vaccine decision-making: A comparative case study of Armenia, Ghana, Indonesia, Nigeria, Senegal and Uganda. Vaccine. 2018; 36, 5536–5543.

78. Howard N et al. The need for sustainability and alignment of future support for National Immunization Technical Advisory Groups (NITAGs) in low and middle-income countries. HUMAN VACCINES & IMMUNOTHERAPEUTICS 2018, 0(0): 1-3. https://doi.org/10.1080/21645515.2018.1444321.

79. Homma, et al. Vaccine research, development, and innovation in Brazil: A translational science perspective. Vaccine. 2013; 31, supp. 2, B54-B60.

80. Houweling, et al. Criteria for inclusion of vaccinations in public programs. Vaccine. 2010; 9;28(17):2924-31.

81. Hsiao, et al. Lessons learnt from 12 oral cholera vaccine campaigns in resource-poor settings. Bull World Health Organ. 2017;95(4):303-312.

82. Hurisa, et al. Production of Cell Culture Based Anti- rabies Vaccine in Ethiopia. Procedia in Vaccinology. 2013;7:2-7.

83. Hyde, et al. The impact of new vaccine introduction on immunization and health systems: A review of the published literature. Vaccine. 2012; 30, 6347– 6358.

84. Jira. Health Ethics and Health Laws: LECTURE NOTES For Health Extension Trainees in Ethiopia. Ethiopia Public Health Training Initiative. 2004.

85. Jit, et al. The broader economic impact of vaccination: reviewing and appraising the strength of evidence. BMC Medicine. 2015; 13:209.

86. Jit and Hutubessy. Methodological Challenges to Economic Evaluations of Vaccines: Is a Common Approach Still Possible? Appl Health Econ Health Policy. 2016; 14:245–252.

87. Kaddar, et al. Global support for new vaccine implementation in middle-income countries. Vaccine. 2013; (31), supp.2:B81-96.

88. Kallenberg, et al. Gavi's Transition Policy: Moving From Development Assistance To Domestic Financing Of Immunization Programs. HEALTH AFFAIRS. 2016;35(2).

89. Kapuria, et al. Designing and implementing an intelligent vaccine logistics management system for India's Universal Immunization Program (UIP) - 'The eVIN Model' Journal of Pharmaceutical Policy and Practice. 2014; 7(Suppl 1):03.

90. Kling and Zeichner. The role of the human papillomavirus (HPV) vaccine in developing countries. Int J Dermatol. 2010;49(4):377-9.

91. Kling, et al. Challenges and Future in Vaccines, Drug Development, and Immunomodulatory Therapy. Ann Am Thorac Soc. 2014; 11(Sup 4): S201-S210.

92. Kitaw. Afterword: Perspectives on future new vaccine introductions in Ethiopia. Ethiop J Health Dev. 2015; 29(Special Issue 1): 31-35.

93. Kitaw, et al. Evolution of Human Resources for Health in Ethiopia, 1941-2010. EPHA, 2014 Addis Ababa pp 327.

94. Kitaw, et al. The Evolution of Public Health in Ethiopia: 1941-2015. Third Revised Edition, EPHA, Addis Ababa, 2017, pp 378.

95. Kitaw and Kaaba. A Century after Yehuda Beset [The Spanish Flu in Ethiopia]: Are We Prepared for the Next Pandemic? Ethiop J. Health Dev. 2018;32(1):74-77.

96. Kochharand Seeber. Introducing new vaccines in developing countries. Expert Rev. Vaccines. 2013;12(12), 1465–1478.

97. Kristensen and Zaffran. Designing vaccines for developing-country populations: ideal attributes, delivery devices, and presentation formats. Procedia in Vaccinology. 2010; 2, 119–123.

98. Kristensen and Chen. Strategies to advance vaccine technologies for resource-poor settings. Vaccine.2013; 31, supp.2; B157-B162.

99. Kurk, et al. Mortality due to low-quality health systems in the universal health coverage era: a systematic analysis of amenable deaths in 137 countries. The Lancet. 2018; 17;392(10160):2203-2212.

100. Larson HJ. Film**:** A global girl gang. The Lancet 2018,391: 527-528.

101. Lee and McGlone. Pricing of new vaccines. Human Vaccines. 2010; 6:8, 619-626.

102. Lee, et al. The estimated mortality impact of vaccinations forecast to be administered during 2011–2020 in 73 countries supported by the GAVI Alliance. PLOS Neglected Tropical Diseases. 2017; 11(10): e0006037.

103. Le Gargasson, et al. Costs of routine immunization and the introduction of new and underutilized vaccines in Ghana. Vaccine. 2015;33 Suppl 1:A40-6.

104. Larson. The State of Vaccine Confidence 2016: Global Insights Through a 67-Country Survey. E Bio Medicine. 2016; 12, 295–301.

105. Lei, et al. Use of a new global indicator for vaccine safety surveillance and trends in adverse events following immunization reporting 2000–2015. Vaccine. 2018; 36,1577–1582.

106. Levine, et al. A policy framework for accelerating adoption of new vaccines. Hum Vaccin. 2010; 6(12): 1021–1024.

107. Lloyd and Cheyne. The origins of the vaccine cold chain and a glimpse of the future. Vaccine. 2017; 19;35(17):2115-2120.

108. Loharikar, et al. Status of New Vaccine Introduction — Worldwide, September 2016. Morbidity and Mortality Weekly Report. 2016; 65 (41): 1136-1140.

109. Loharikar. Global Introduction of New Vaccines: Delivering More to More. Centers for Disease Control and Prevention. March, 2018.

110. Luyten, et al. Public Preferences for Prioritizing Preventive and Curative Health Care Interventions: A Discrete Choice Experiment. Value in Health. 2015; 18,224 – 233.

111. Lydon, et al. Health system cost of delivering routine vaccination in low- and lower-middle income countries: what is needed over the next decade? Bulletin of the World Health Organization. 2014; 92:382-4.

112. Lydon, et al. Vaccine stockouts around the world: Are essential vaccines always available when needed? Vaccine. 2017; 35, 2121–2126.

113. Mackenzie, et al. Monitoring the Introduction of Pneumococcal Conjugate Vaccines into West Africa: Design and Implementation of a Population-Based Surveillance System. PLoS Med. 2012; 9(1): e1001161.

114. MacLennan. Vaccines for low-income countries. Seminars in Immunology. 2013; 25, 114– 123.

115. MacLennan and Saul. Vaccines against poverty. PNA. 2014; 111(34): 12307-12312.

116. Madhavan, et al. Bridging the gap: need for a data repository to support vaccine prioritization efforts. Vaccine. 2015; 8; 33(0 2): B34–B39.

117. Makinen, et al. New vaccine adoption in lower-middle-income Countries. Health Policy and Planning. 2012;27, sup.2,ii39-49.

118. Mantel and Wang. The privilege and responsibility of having choices: decision-making for new vaccines in developing countries. Health Policy and Planning. 2012;27:ii1–ii4.

119. Masters, et al. Vaccine hesitancy among caregivers and association with childhood vaccination timeliness in Addis Ababa, Ethiopia. Human Vaccine and Immuno-therapeutics. 2018; 14 (10), pp.2340-2347.

120. Maxmen A. Malaria vaccine rolled out in Africa, but doubts linger. Nature 2019, 569:14-15.

121. MCHIP. Bottlenecks and Breakthroughs: Lessons Learned from New Vaccine Introductions in Low-resource Countries, 2008 to 2013. Maternal Child Health Integrated Program (MCHIP), U.S. Agency for International Development, 2014.

122. McQuestion, et al. Creating Sustainable Financing and Support For Immunization Programs In Fifteen Developing Countries. Health Affairs. 2011;30(6).

123. Mihigo, et al. Investing in life saving vaccines to guarantee life of future generations in Africa. Vaccine. 2016; 34, 5827–5832.

124. Mihigo, et al. Challenges of immunization in the African region. The Pan African Medical Journal. 2017;27 (Supp 3):12.

125. Milstien and Belgharbi. Regulatory pathways for vaccines for developing countries. Bulletin of the World Health Organization. 2004;82:128-133.

126. MOH. Comprehensive multi-year plan 2016 – 2020. April 2015; Addis Ababa.

127. MOH. 'Federal Ministry of Health of Ethiopia. Health Sector Transformation Plan', Federal Ministry of Health (FMOH). 2015; Addis Ababa, Ethiopia; from http://www.globalfinancingfacility.org/sites/gff_new/files/documents/HSTP%20Ethiopia.pdf.

128. MOH. 2015a, MOH, 2015a, '*Envisioning Ethiopia's Path towards Universal Health Coverage through strengthening Primary Health Care',* Federal Ministry of Health (FMOH), Addis Ababa, Ethiopia.

129. Makenga G, Bonoli S, Montomoli E, Carrier T, Auerbach J. Vaccine Production in Africa: A Feasible Business Model for Capacity Building and Sustainable New Vaccine Introduction. Front. Public Health, 20 March 2019. Accessed July 2019 at *https://doi.org/10.3389/fpubh.2019.00056*

130. Mogasale, et al. A forecast of typhoid conjugate vaccine introduction and demand in typhoid endemic low- and middle-income countries to support vaccine introduction policy and decisions. Hum Vaccin Immunother. 2017; Sep 2;13(9):2017-2024.

131. Moher, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. J Clin Epidemiol. 2009;62:1006–12.

132. Molina-Aguilera. Perspectives on the development and use of economic evidence for immunization decision-making in a developing country. Vaccine. 2015;285:A6-A7.

133. Molla, et al. New Vaccine Adoption and Decision Making in Ethiopia: Qualitative Study of National Decision-Making Processes for the introduction of PCV 10. Ethiop J Health Dev. 2015; 29(Special Issue 1): 17-22.

134. Molla, et al. Impacts of accelerated measles elimination activities on immunization services and the general health system in Ethiopia. Ethiop J Health Dev. 2015; 29(Special Issue 1): 23-30.

135. Moxon and Siegrist. The next decade of vaccines: societal and scientific challenges. Lancet. 2011; 378: 348–59.

136. Nader, et al. An analysis of government immunization program expenditures in lower and lower middle income countries 2006–12. 2014. *Health Policy and Planning. 2015;*30 (3), pp. 281–288.

137. Nannei, et al. Considerations for sustainable influenza vaccine production in developing countries. Vaccine. 2016;34(45): 5425-5429.

138. Nelson, et al. Monitoring What Governments ''Give for'' and ''Spend on'' Vaccine Procurement: Vaccine Procurement Assistance and Vaccine Procurement Baseline. PLoS ONE. 2014; 9(2): e89593.

139. Nelson, et al. Assessing strategies for increasing urban routine immunization coverage of childhood vaccines in low and middle-income countries: A systematic review of peer-reviewed literature. Vaccine. 2016; 34(46):5495-5503.

140. Newall and Hutubessy. Are Current Cost-Effectiveness Thresholds for Low- and Middle-Income Countries Useful? Examples from the World of Vaccines. Pharmacoeconomics. 2014;32(6):525-31.

141. Ngcobo and Cameron. The decision making process on new vaccines introduction in South Africa. Author information. Vaccine. 2012;30, Suppl 3:C9-13.

142. NossaL. Vaccines and future global health needs. Phil. Trans. R. Soc. B (2011) 366, 2833–2840. doi:10.1098/rstb.2011.0093

143. Olayinka, et al. Beyond new vaccine introduction: the uptake of pneumococcal conjugate vaccine in the African Region. The Pan African Medical Journal. 2017;27 (Supp.3):3.

144. Olsson, et al. Pharmacovigilance in resource-limited countries, Expert Review of Clinical Pharmacology. 2015; 8:4, 449-460.

145. Oyo-Ita A, et al. Interventions for improving coverage of childhood immunization in low- and middle-income countries (Review). Cochrane Database Syst Rev. 2016; Jul 10;7:CD008145.

146. Ozawa, et al. Return On Investment From Childhood Immunization In Low- And Middle-Income Countries, 2011–20. Health Affairs. 2016; 35, No. 2: 199–207.

147. Pagliusi, et al. The DCVMN Executive Committee Group. Vaccines, our shared responsibility. Vaccine. 2015;33(19):2197-2202.

148. Pagliusi, et al. Quality vaccines for all people. Report of the annual general meeting of the developing countries vaccine manufacturers' network, 05–07th October 2015, Bangkok, Thailand. Vaccine. 2016; 34:3106 (30), pp.3562-7.

149. Peter, et al. New Vaccines for the World's Poorest People. Annual Review of Medicine. 2016;67:405-417.

150. Pichichero. Pneumococcal whole-cell and protein-based vaccines: changing the paradigm. Expert Review of Vaccines. 2017; 16:12, 1181-1190.

151. Plotkin, et al. The complexity and cost of vaccine manufacturing-An overview. Vaccine. 2017;24;35(33):4064-4071.

152. Postma and Standaert. Economics of vaccines revisited, Human Vaccines & Immunotherapeutics. 2013; 9:5, 1139-1141.

153. R4D. Immunization financing: a resource guide for advocates, policymakers, and program managers. Washington D.C.: Results for Development; 2017.

154. Rappuoli, et al. Vaccines for the twenty-first century society. Nat Rev Immunol. 2011; 11(12):865-72.

155. Rees and Madhi. Will the Decade of Vaccines mean business as usual? The Lancet. 2011; 378: 382-384.

156. Restrepo-Méndez MC et al. Inequalities in full immunization coverage: trends in low- and middle-income countries. *Bull World Health Organ* 2016;94:794–805A .

157. Ricciardi, et al. Comparison of NITAG policies and working processes in selected developed countries. Vaccine. 2015; 33: 3-11.

158. Romore, et al. Policy analysis for deciding on a malaria vaccine RTS, S in Tanzania. Malaria Journal. 2016; 15, 143.

159. Rueda-Torres, et al. Introduction of PCV-10 in Ethiopia: Effects on the Health System. Ethiop J Health Dev. 2015; 29(Special Issue 1): 8-16.

160. Sadnand. Vaccination: the Present and the Future. Yale Journal of Biology and Medicine. 2011; 84, pp.353-359.

161. SAGE. National Immunization Technical Advisory Groups: Background Paper. April 2017.

162. Scorza, et al. Universal influenza vaccines: Shifting to better vaccines. Vaccine. 2016; 34(26): 2926–2933.

163. Shen, et al. Country Ownership and Gavi Transition: Comprehensive Approaches To Supporting New Vaccine Introduction. Health Affairs. 2016;35(2).

164. Shin, et al. Oral Vaccines Against Cholera. *Clin Infect Dis. 2011;*52(11) 1343–1349.

165. Storrs. As Oral Vaccines Fall Short In Low-Income Countries, Researchers Look For Solutions. Health Affairs. 2016; 35,(2):317-321.

166. SVI.. A Decade of Sustainable Immunization Financing. Sabin Vaccine Institute, Washington, D.C.; 2019.

167. Tadesse, et al. Factors and misperceptions of routine childhood immunization service uptake in Ethiopia: findings from a nationwide qualitative study. The Pan African Medical Journal. 2017;28:290.

168. Tekki IS, Nwosu C, Okewole PA. Challenges and prospects of anti-rabies vaccines production in Nigeria. *J Vaccines Vaccin* 2013; 4:8 DOI: 10.4172/2157-7560.1000212

169. Torres-Rueda, et al. New pneumococcal conjugate vaccine introduction in four sub-Saharan African countries: a cross-country analysis of health systems' impacts. Afri Health Sci. 2015;15(3):868-77.

170. Turner. Immunization – a global issue Update from SAGE. WHO, 2016.

171. Uddinet al. Introduction of New Vaccines: Decision-making Process in Bangladesh. J Health Popul Nutr. 2013;31(2): 211–217.

172. UNDP. A Pipeline Analysis of New Products for Malaria, Tuberculosis and Neglected Tropical Diseases: A working paper. UNDP 2016.

173. Utazi, et al. High resolution age-structured mapping of childhood vaccination coverage in low and middle income countries. Vaccine. 2018; 36,1583–1591.

174. Wallace and Kapirir. How Are New Vaccines Prioritized in Low-Income Countries? A Case Study of Human Papilloma Virus Vaccine and Pneumococcal Conjugate Vaccine in Uganda. Int J Health Policy Manag. 2017;12: 707–720.

175. Walwyn DR. Why manufacturing a key vaccine in South Africa is so important? *The Conversation* 2016 [Available at: http://theconversation.com/why-manufacturing-a-key-vaccine-in-south-africa-is-so-important-94380]

176. Wang, et al. New vaccine introductions: Assessing the impact and the opportunities for immunization and health systems strengthening. Vaccine. 2013;31(0 2): B122–B128.

177. WHO. Resolution of the 61st World Health Assembly. Geneva, World Health Organization, 2008.

178. WHO. The Initiative for Vaccine Research: Strategic plan 2010–2020. World Health Organization. 2010; Geneva.

179. WHO. Global vaccine action plan 2011-2020. World Health Organization. 2013; Geneva.

180. WHO. Report of the SAGE working group on vaccine hesitancy. 2014.

181. WHO. Explorations of inequality: childhood immunization. World Health Organization. 2018; Geneva.

182. WHO. WHO vaccine-preventable diseases: monitoring system. 2018 global summary. 2018, Geneva.

183. WHO. Global Vaccine Action Plan. Monitoring, Evaluation & Accountability. Secretariat Annual Report 2018. Geneva: World Health Organization. 2018a. Licence: CC BY-NC-SA 3.0 IGO.

184. WHO. 2018 Assessment report of the Global Vaccine Action Plan. Strategic Advisory Group of Experts on Immunization. Geneva: World Health Organization. 2018b (WHO/IVB/18.11). Licence: CC BY-NC-SA 3.0 IGO.

185. WHO. Working together: an integration resource guide for immunization services throughout the life course. Geneva: World Health Organization; 2018. Licence: CC BY-NC-SA 3.0 IGO.

186. WHO AFRO. Roadmap for Implementing the Addis Declaration on Immunization: Advocacy, Action, and Accountability. World Health Organization, Regional Office for Africa, June 2017.

187. WHO AFRO. Guide for developing national immunization policies in the WHO African Region. World Health Organization, Regional Office for Africa, 2017, Brazzaville.

188. WHO, UNICEF, World Bank. *State of the world's vaccines and immunization*, 3rd ed. Geneva, World Health Organization, 2009.

189. Williams, et al. The composition of demand for newly launched vaccines: results from the pneumococcal and rotavirus vaccine introductions in Ethiopia and Malawi. Health Policy and Planning. 2016; 31, 563–572.

190. Young, et al. Developing new health technologies for neglected diseases: a pipeline portfolio review and cost model. Gates Open Research. 2018;2:23.

191. Zewdie, et al. Reasons for defaulting from childhood immunization program: a qualitative study from Hadiya Zone, Southern Ethiopia. BMC Public Health. 2016; 16:1240.

192. Zuber, et al. Sustaining GAVI-supported vaccine introductions in resource-poor countries. Vaccine. 2011;12;29(17):3149-54.

Appendix 1: Themes for the scoping review

1. Currently available vaccines: Types, Availability, Cost, Implementation modality …
    1.1. Currently in use in Ethiopia? How?
    1.2. Not currently in use in Ethiopia: Which are relevant (Disease burden Acceptability, Delivery system requirements, HRH implications, Financing …) to Ethiopia?
2. New/new generation Vaccines (next 10 years?)
    2.1. Vaccines are on the horizon (Types, Availability, Cost, Implementation modality…)
    2.2. Issues of introducing in Ethiopia (Disease burden, Acceptability, Delivery system requirements, HRH implications, Financing …)
3. Potential problems/challenges of introducing new/unutilized vaccines in low-middle-income countries/Ethiopia
    3.1. Socio-economic/financial challenges
    3.2. 'health system' (policy, HRH, logistics management, implementation, processes…) challenges…
4. Potential opportunities and lessons to be leveraged
    4.1. Socio-economic/financial opportunities
    4.2. 'health system' (policy, HRH, logistics management, implementation, processes ...) opportunities
5. Vaccine intelligence modalities-
    5.1. Country/ regional/international experiences
    5.2. Ethiopian experiences
6. Introduction processes
    6.1. Pre-Introduction Decisions
        6.1.1. Selecting the Vaccine Product
        6.1.2. Deciding Who Is Eligible For the New Vaccine
        6.1.3. Revising the Immunization Schedule
    6.2. Preparing for the Vaccine Introduction

6.2.1. Establishing Organizational Structures to Prepare for New Vaccine Introduction

6.2.2. Budgeting and Securing Funding For New Vaccine Introduction and the Long Term

6.2.3. Determining Country Readiness and Appropriate Timing for Vaccine In troduction

6.2.4. Assessing, Upgrading and Expanding Cold Chain, Logistics, and Waste Management Systems to Accommodate New Vaccines

6.2.5. Revising Vaccine Management Systems to Accommodate New Vaccines

6.2.6. Building Health Worker Capacity for Safe and Effective Use of Vaccines

6.2.7. Communicating and Creating Demand for New Vaccines and Immunization

6.2.8. Revising Health and Immunization Management and Reporting Forms and Materials to Include the New Vaccine

6.3. Monitoring and Evaluating the Vaccine Introduction

6.3.1. Coverage Monitoring For the New Vaccine

6.3.2. Post-Introduction Program Monitoring and Supervision

7. Others (specify) _____

Appendix 2: Questions for Key Informant (KI) Interviews[8]

1. How do you assess the current immunization system in the country? (SWOT)

   1.1. Any envisaged change in immunization schedule?

      1.1.1. What vaccines are included and how?

      1.1.2. Any change in supply system?

   1.2. Logistics and Cold chain issues?

   1.3. Coverage and HRH issues?

   1.4. Governance and management?

      1.4.1. Issues in information/mobilization/ownership, policy/strategy/planning, legislation (mandatory or recommended?), the decentralized system, inequality in coverage…

      1.4.2. Any threats from 'vaccine hesitancy', growing public mistrust and the rise of so-called "fake news"

   1.5. Financing issues?

   1.6. Overall impact (strengthening, weakening…) on the immunization program and the health system?

2. How do you see the introduction of new vaccines in the future?

   2.1. How were the decisions to introduce recent new vaccines (PCV, Rota, HPV...) taken

      2.1.1. Disease burden, Acceptability, Delivery system requirements, HRH impli cations, HMIS, Financing …? Any lessons?

      2.1.2. Who participated in the decision-making process (other sectors, NGOs, private sector, professional organizations, partners, RHBs, WeHO …)?

   2.2. Are new vaccine introductions being envisaged? Any on the horizon - Types, Availability, Cost, Implementation modality… (Annex Table 2)?

   2.3. What could be the problems/challenges of introducing new/unutilized vaccines in Ethiopia? Any opportunities? (including experiences from other low-mid dle-income countries)

      2.3.1. Socio-economic challenges? (Large country, large/diverse population,

8 To be adapted to type of KI; current essentially for Ethiopian officials

poor socio-economic development…)

2.3.2. 'health system' - policy, under-utilization, HRH (ability to handle complex vaccine environment, familiarity with best practices in supply chain man agement), logistics management (vaccine wastage and inadequate immunization coverage, adequate cold chain…), implementation, processes (safe immunization practices, monitoring adverse events …), quality M&E, VMIS, resource, performance and management account ability … challenges

2.3.3. Financing (potential sources, sustainability…)

2.3.4. Opportunities/lessons …

2.4. Is the decision-making mechanism adequately institutionalized? (elaborate, how strong? Any improvement?); role of:

2.4.1. Regulatory Authority ('FMHACA'?)

2.4.2. Advisory Committee (NITAG?)

2.4.3. Inter-agency Coordinating Committee?

2.4.4. ARM?

2.4.5. ..

3. Any other thoughts/recommendations on

3.1. Introduction of new vaccines?

3.2. Establishing/strengthening vaccine intelligence system in Ethiopia?

3.3. Establishing/strengthening vaccine research/evidence-base system?

3.4. Additional resources (KI, documents…) to strengthen the study?

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